Impacts of skill training on swallowing and quality of life in patients with motor neurone disease

A Thesis Submitted in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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Abstract

Motor neurone disease (MND) is a neurodegenerative disease with reported incidence between 1.68 and 2.08 per 100,000 (A Chio et al., 2013; Marin et al., 2017) and prevalence of 5.40 per 100,000 (A Chio et al., 2013). The defining symptoms of MND are loss of voluntary control of muscle movement, spasticity and hyperreflexia due to degeneration of upper motor neurons, and flaccidity, atrophy and fasciculations due to degeneration of lower motor neurons. These symptoms can affect the muscles of deglutition, resulting in oropharyngeal dysphagia. Patients with MND are not often offered dysphagia treatment due to a historical belief that exercise would result in muscular fatigue and increased rate of degeneration (Plowman, 2015). However, recent research demonstrates that low to moderate intensity exercise may be beneficial for patients with MND (Carreras et al., 2010; Plowman, 2015). Additional research is necessary to determine appropriate treatment modalities to improve swallowing outcomes in this population. The research presented in this thesis investigated the effects of skill training on swallowing and quality of life outcomes in patients with MND. This programme of research involves a methodological study investigating quantification of fatigue during exercise of bulbar muscles and two exploratory studies that investigated the effects of skill training for swallowing.

Study one investigated the potential for using surface electromyography (sEMG) as a method of quantifying fatigue of bulbar muscles during a lingual pressure endurance task. It is known that as muscles become fatigued, additional motor units are recruited, firing frequency increases and discharges are synchronised for sustained power generation (Chang, Chablat, Bennis, & Ma, 2016). However, it is unknown whether the smoothed data from sEMG of the submental muscles can be used during a lingual pressure task to indicate degree of muscular fatigue. Twenty-four healthy participants completed a lingual endurance task with sEMG placed over the submental muscles. Results demonstrated fatigue over the task, represented by a gradual decline in endurance time. However, there was no significant difference in average sEMG output across sessions, indicating that sEMG of the submental muscles, as used in this study, is not an appropriate method of quantifying fatigue during a lingual pressure task.

The second and third studies were exploratory studies that first assessed the feasibility of a skill training protocol in patients with MND and then assessed the effect of the treatment on

biomechanical, functional and quality of life outcomes. The aim of the pilot study was to determine whether further research was possible within the New Zealand context and to refine the methodology of the treatment study. Five participants underwent a four-week skill training protocol with a four-week no contact periods pre-treatment (baseline) and post-treatment (retention). The skill training protocol consisted of 80 swallows per session using the Biofeedback in Strength and Skill Training (BiSSKiT) software. BiSSkiT uses surface electromyography (sEMG) for visualisation of muscle activity to enhance conscious control of swallowing. There were no drop outs and all participants were able to follow instructions to complete the treatment task. Following treatment, an improvement in functional swallowing was observed for the patients with mild to moderate dysphagia. This improvement was demonstrated through increased volume swallowed per second, increased swallowing efficiency and decreased time per swallow when consuming 150 mL of water in the Timed Water Swallow Test (TWST). These findings indicated that further research was warranted.

The treatment study followed the pilot study and investigated additional outcome measures including biomechanical changes to swallowing. For the treatment study, 27 patients with MND were recruited. From these participants, 19 completed two weeks of daily skill training using the BiSSkiT software with a two-week baseline and two-week retention period. Quality of life was measured through the Swallowing Quality of Life Questionnaire (Swal-QOL), functional swallowing assessed through the TWST and the Test of Masticating and Swallowing Solids (TOMASS). Additionally, instrumental assessments (ultrasound [US], videofluoroscopy [VF] and high resolution impedance manometry [HRIM]) were included to assess swallowing biomechanics. Following treatment, timing ($p < .01$) and amplitude ($p = .04$) errors during the skilled task decreased, total symptom frequency measured by the Swal-QOL improved ($p = .02$) and oropharyngeal transit time decreased for puree ($p = .01$) but increased for water ($p = .02$). Hyoid displacement on VF increased over the retention period but not the treatment period for water ($p = .04$) and puree ($p = .01$). Although there was evidence of improvements in quality of life and swallowing biomechanics, there were no significant differences observed in functional swallowing outcomes. This research demonstrates that participants with MND are able to participate in swallowing skill training and improve at the task with no evidence of adverse effects. Changes in quality of life and swallowing biomechanics were observed following two weeks of treatment; however, there was no transfer to functional tasks. This suggests two weeks of treatment is not sufficient for

functional improvement but may have facilitated maintenance of function and highlights the need for future research.

Skill training is a developing area of treatment for dysphagia. This research was the first to investigate the use of skill training to improve pharyngeal swallowing for patients with MND. Results from these studies add to the emerging literature that demonstrates the need for alternative options to traditional strength based treatment for patients with dysphagia.

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Contents

Preface

This thesis follows the referencing style of the American Psychological Association (6th edition) and the spelling recommended by the Oxford English Dictionary.

The research in this thesis was conducted between March 2016 and September 2020 at the University of Canterbury Rose Centre for Stroke Recovery and Research at St. Georges Medical Centre, the Upper Airway Dysfunction Laboratory at Teacher's College, Columbia University and North Shore Hospital, Waitemata DHB. Financial support was provided by the College of Science Doctoral Scholarship and Fulbright Science and Innovation Grant.

Preliminary results from the research presented in this thesis have been presented at the following conferences:

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In addition to the research presented in this thesis, over the course of enrolment, collaboration and data collection/extraction occurred for the following studies:

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Winiker, K., Burnip, E., Gozdzikowska, K., Esther Guiu Hernandez, E., Hammond, B., Macrae, M., **Thomas, P**., Wilson, R., Huckabee, M.L. Reliability of a pocket-sized system in the assessment of swallowing. Manuscript in prep.

List of abbreviations

ALS: Amyotrophic Lateral Sclerosis

ALSFRS-R: Amyotrophic Functional Rating Scale -Revised

BiSSKiT: Biofeedback in Strength and Skill Training

CI: cognitive impairment

CN: cranial nerve

CPG: central pattern generator

CSA: cross sectional area

CTAR: chin tuck against resistance

DIGEST: dynamic imaging grade of swallowing toxicity

Df: degrees of freedom

DSS: dynamic swallow study

EAT-10: 10 item Eating Assessment Tool

EMST: Expiratory muscle strength training

FEES: fibreoptic endoscopic evaluation of swallowing

fMRI: functional magnetic resonance imaging

fNIRS: function near-infared spectroscopy

FVC: forced vital capacity

GH: geniohyoid muscles

H_{rest}: hyoid position at rest

H_{max}: hyoid position at maximum displacement

HPTT: hypopharyngeal transit time

HR(I)M: high resolution (impedance) manometry

ICC: intraclass correlation coefficient

LAR: laryngeal adduction reflex

LMN: lower motor neurons

LAB/RAB: Left anterior belly/ right anterior belly of the digastric muscles

MEG: magnetoencephalography

MEP: maximum expiratory pressure

MIP: maximum isometric pressure

MND: Motor Neurone Disease

MoCA: Montreal Cognitive Assessment

MRI: magnetic resonance imaging

μV: microvolts

NA: Nucleus ambiguus

NIV: non-invasive ventilation

NTS: Nucleus tractus solitarius

OPTT: oropharyngeal transit time

PA_{rest}: pharyngeal area at rest

PA_{max}: pharyngeal area at maximum constriction

PAS: penetration aspiration scale

PCR: pharyngeal constriction ratio

PEG: percutaneous endoscopic gastrostomy

PP: pharyngeal plexus

RLN: recurrent laryngeal nerve

sEMG: surface electromyography

Swal-QOL: Swallowing quality of life assessment

SLN: superior laryngeal nerve

SLT: speech-language therapist/ speech-language therapy.

TOMASS: Test of Masticating and Swallowing Solids

TPTT: total pharyngeal transit time

TWST: Timed Water Swallow Test

UES: upper esophageal sphincter

UMN: upper motor neurons

VFSS: videofluoroscopic swallowing study

PART I: INTRODUCTION AND LITERATURE REVIEW

1. Introduction

Dysphagia is a common symptom associated with MND (A. Chen & Garrett, 2005; Kühnlein et al., 2008; Onesti et al., 2017). Oropharyngeal dysphagia can result in malnutrition and aspiration pneumonia, which can lead to death (Corcia et al., 2008; Yang et al., 2011). Dysphagia is also one of the biggest contributors to reduced quality of life (Paris et al., 2013). Patients with MND often do not complete exercises to improve dysphagia due to a historic belief that exercise results in fatigue of muscles and leads to a hastened rate of decline. However, recent evidence demonstrates that mild-moderate intensity exercise may be beneficial for maintaining strength and functional ability in patients with MND; this includes exercise of bulbar muscles (Carreras et al., 2010; Plowman, 2015; Plowman et al., 2019). Swallowing is a task that is performed at submaximal strength and adverse effects such as nasal redirection and a reduction in hyoid excursion have been associated with strength training (Bülow, Olsson, & Ekberg, 1999; Garcia, Hakel, & Lazarus, 2004). There is the need for further investigation to identify appropriate treatment options for managing dysphagia in this population. Skill training has been investigated in the limb literature for decades but is a recent addition to dysphagia management. The aim of skill training is to enhance neuroplasticity and cortical control of muscle movements. This research programme investigates fatigue of bulbar muscles during endurance tasks and the potential of skill training to improve swallowing and quality of life outcomes for patients with MND.

Part I is a comprehensive literature review. A summary of the physiology and neural control of normal swallowing is provided in chapter two. Chapter three discusses MND, including the pathophysiology associated with dysphagia and the effects of dysphagia on health outcomes and quality of life. Routine intervention in MND is discussed in chapter four and chapter five discusses dysphagia assessment. Current methods for managing dysphagia and emerging evidence for potential treatment options are discussed in chapter six along with the strengths and limitations of treatment approaches. Chapter seven provides a summary of the evidence.

Part II presents the experimental studies. Chapter eight summarises the objectives and hypotheses for the studies that are discussed in this thesis. The first is a methodological study, discussed in chapter nine. This study investigates the use of clinically replicable measures of surface electromyography (sEMG) for quantifying fatigue of bulbar muscles during a series

of lingual presses. This study is somewhat peripheral but related to the overall theme of the thesis, as fatigue is a limiting factor in many treatment options for patients with MND. Quantification of fatigue may help to ensure that patients are completing exercises at a level that allows them to receive maximum benefit without reaching an intensity that results in detrimental muscle fatigue. The study was designed as a community engagement protocol to introduce two high school students to research.

Chapter 10 describes an exploratory investigation into the use skill training to improve swallowing and quality life outcomes in patients with MND. This includes two exploratory studies that were inspired by a lack of treatment options for dysphagia offered to patients with MND and the limitations associated with strength training. This section consists of a pilot study investigating the feasibility and safety of using skill training for this patient population and a treatment study that investigated changes in functional, biomechanical and quality of life outcomes associated with skill training. These studies are important steps in assessing potential treatment options to improve dysphagia outcomes for patients with this degenerative neurological disease. Chapter 11 provides the concluding remarks from this thesis, and discussed how the research programme has contributed to the current literature in treatment options for patients with MND.

2. Normal swallowing

Swallowing is a complex biomechanical process that involves the coordinated recruitment of 31 pairs of muscles (Dodds, Stewart, & Logemann, 1990). This highly coordinated sequence of muscle contractions is vital for adequate nutritional intake and pulmonary safety. Safety and efficiency are not dependent on motor movements alone; sensory feedback is integrated at all stages of swallowing to ensure precision of movement and to allow the process to adapt to differences in bolus density, viscosity and size.

2.1 Phases of swallowing

Swallowing is often broken down into phases based on visual analysis of bolus position and physiological response. There is a large amount of overlap between the interdependent phases (Martin-Harris, Michel, & Castell, 2005), making the boundaries of each distinct phase open for interpretation. For the purposes of this document, swallowing will be described in four discrete stages: the pre-oral, oral, pharyngeal and oesophageal phases, as described by Daniels and Huckabee (2014). An overview of normal swallowing is provided; however, it is important to consider that there is a large amount of variation encompassed in normal swallowing behaviour. Differences in swallowing have been demonstrated in relation to age and sex, as well as a large amount of variation both within and between individuals (Robbins, Hamilton, Lof, & Kempster, 1992).

2.2 Pre-oral phase of swallowing

The process of swallowing begins prior to placing a bolus in the oral cavity, as sensory receptors from the optic and olfactory cranial nerves activate the cerebral cortex (Ebihara et al., 2006). This pre-oral stimulation allows an individual to prepare for a bolus, and modifies subsequent swallowing by increasing the rate of saliva production by the sublingual, submandibular and parotid glands (Noh, Im, & Kim, 2017; Pedersen, Sørensen, Proctor, Carpenter, & Ekström, 2018). Saliva is important during swallowing as it increases taste, facilitates bolus formation and begins the digestive process of starches and lipids (Pedersen, Bardow, Jensen, & Nauntofte, 2002). Additionally, pre-oral olfactory and optic stimulation can result in increased appetite and reduced latency of the onset of pharyngeal swallowing, improving swallowing outcomes (Ebihara et al., 2006; Maeda et al., 2004; Munakata et al., 2008).

2.2.1 Oral phase of swallowing

The oral phase begins once a bolus is placed within the oral cavity. During this phase, oral containment of the bolus is crucial. Multiple muscles are recruited to contain the bolus both anteriorly and posteriorly. Anterior bolus containment is important to prevent bolus loss through the lips. This is achieved through contraction of the orbicularis oris muscle, which ensures that there is adequate labial seal (Daniels & Huckabee, 2014). Glossopalatal approximation is necessary to prevent the bolus from spilling into the pharynx prior to the initiation of swallowing (J. Cichero, 2006; Daniels & Huckabee, 2014). Premature spillage of the bolus into the pharynx can result in pre-swallow aspiration if airway closure is not complete.

During the oral phase of swallowing, a cohesive bolus is formed by breaking down food into small particles and mixing it with saliva from the submandibular, sublingual and parotid glands. The intrinsic lingual muscles move the bolus around the mouth and between the teeth, such that mastication can prepare a solid bolus for swallowing. Jaw opening occurs through contraction of the anterior belly of the digastric, mylohyoid and geniohyoid muscles, in conjunction with relaxation of muscles required to close the jaw. The temporalis, masseter and medial pterygoid muscles are necessary for jaw closing, and the lateral pterygoid muscles for jaw lateralisation (J. A. Cichero & Murdoch, 2006). Mastication is largely a repetitive, rhythmic movement produced by a central pattern generator within the brainstem. However, the pattern of mastication can be altered, both by conscious control and sensory feedback (Lund & Kolta, 2006). Sensory feedback is necessary to ensure that the cheeks and tongue do not fall between the teeth, to alter bite force dependent on the hardness of the food and to provide information about the position of the bolus and its readiness for safe transfer to the pharynx.

Glossopalatal approximation is maintained throughout the oral preparatory phase to ensure the bolus remains in the oral cavity. Once the bolus is adequately prepared for transfer to the pharynx, the palatoglossus muscles relax to drop the base of tongue and the genioglossus and hyoglossus muscles pull the base of tongue inferiorly. The intrinsic and extrinsic lingual muscles then pull the tongue up, to approximate the palate anteriorly to posteriorly. This helps to squeeze the bolus out of the oral cavity and into the pharynx to begin the pharyngeal phase of swallowing (Daniels & Huckabee, 2014; Kahrilas, Lin, Logemann, Ergun, & Facchini, 1993; Matsuo & Palmer, 2015).

2.2.2 Pharyngeal phase of swallowing

The definition of the onset of the pharyngeal response has been debated in the literature. Bolus entry to the pharyngeal space is not a reliable indicator of swallowing onset as it is highly variable. Bolus position is dependent on factors such as single vs. sequential swallows and whether a command of when to swallow is provided (Daniels, Schroeder, DeGeorge, Corey, & Rosenbek, 2007; Steele & Miller, 2010; Stephen et al., 2005). Further, the occurrence of pharyngeal aggregation of the bolus, in the absence of other indicators of pharyngeal swallowing onset, is considered normal. This means that in healthy individuals, part of the bolus could be transferred into the pharynx up to 10 seconds prior to initiation of the pharyngeal phase of swallowing, without increased risk of airway invasion (Chi-Fishman & Sonies, 2000; Daniels & Foundas, 2001; Dua, Ren, Bardan, Xie, & Shaker, 1997; Martin-Harris, Brodsky, Michel, Lee, & Walters, 2007; Matsuo, Hiiemae, Gonzalez-Fernandez, & Palmer, 2008). Therefore, the onset of hyolaryngeal excursion is most commonly used to indicate the beginning of the pharyngeal phase of swallowing (Daniels & Huckabee, 2014; Nam, Oh, & Han, 2015).

Once the pharyngeal phase of swallowing is initiated, many overlapping events contribute to the safe and efficient passage of the bolus through the pharynx. Velopharyngeal approximation creates a barrier, separating the nasopharynx from the oropharynx. This assists with pharyngeal pressure generation by preventing loss of pressure through the nose (Kahrilas, 1993). Velopharyngeal approximation is achieved through soft-palate elevation and approximation of the pharyngeal wall, as well as anterior bulging of the adenoid pad (Daniels & Huckabee, 2014; Harrington, 1944). Temporally, velopharyngeal closure occurs as the muscles responsible for glossopalatal approximation relax (Kahrilas et al., 1993). Separation of the oropharynx and nasopharynx remains throughout the pharyngeal phase of swallowing.

Laryngeal valving is necessary to prevent material from entering the laryngeal vestibule during swallowing. There are multiple levels of airway protection that serve as safeguards, should there be dysfunction of one level. Airway protection occurs through approximation of the true and false vocal folds, and epiglottis to arytenoid contact. Activation of the interarytenoid and lateral cricoarytenoid muscles results in adduction of true and false vocal folds (Andaloro & La Mantia, 2019). Deflection of the cartilaginous epiglottis is a result of external forces. The suprahyoid muscles function to pull the hyoid and larynx superiorly and

anteriorly. The submental muscles consist of the bilateral mylohoid, geniohyoid and anterior belly of the digastric muscles. The geniohyoid muscles attach to the hyoid from the inferior mental spine of the mandible. The mylohyoid muscles insert on the mylohyoid line of the mandible; posterior portions of the mylohyoid muscles insert into the body of the hyoid bone and the anterior portions insert into the median raphe that connects the left and right mylohyoid muscles (Shaw et al., 2017). The anterior belly of the digastric muscles run from the intermediate tendon of the digastric muscles to the digastric fossa of the mandible (Shaw et al., 2017). Anterior hyoid excursion through contraction of the submental muscles pulls the base of the epiglottis anteriorly. The larynx is attached to the hyoid bone by the thyrohyoid membrane and thyrohyoid muscles and is pulled up and forwards with the movement of the hyoid. Contraction of the thyrohyoid muscles further pull the larynx up. These collective movements result in the deflection of the epiglottis for airway protection. There is a large amount of variability in the timing of airway closure. If material enters the pharynx prior to the onset of pharyngeal swallowing, partial true vocal fold approximation may occur to prevent aspiration (Dua et al., 1997). However, complete adduction of the vocal folds often does not occur until after hyolaryngeal excursion begins (Inamoto et al., 2011; Ohmae, Logemann, Kaiser, Hanson, & Kahrilas, 1995). Temporally, maximal epiglottic deflection occurs following onset of hyoid excursion, as hyolaryngeal excursion is a necessary facilitator of epiglottic deflection (Inamoto et al., 2011).

Laryngeal closure results in a period of swallowing apnoea. The pattern of inspiration and expiration surrounding swallowing apnoea may impact swallowing safety. In healthy adults, swallowing apnoea can occur mid-expiration, mid-inspiration or at the transitions between inspiration and expiration or expiration and inspiration (Martin-Harris, Brodsky, et al., 2005). However, the most common, and safest, pattern is for swallowing apnoea to occur mid-expiration (Hiss, Treole, & Stuart, 2001; Martin-Harris, Brodsky, et al., 2005; McFarland & Lund, 1995; Paydarfar, Gilbert, Poppel, & Nassab, 1995; J. Smith, Wolkove, Colacone, & Kreisman, 1989). Appropriately timed respiratory swallowing coordination is believed to contribute to increased subglottic pressure as a result of higher lung volume at the time of swallowing (Gross, Atwood Jr, Grayhack, & Shaiman, 2003; Gross, Steinhauer, Zajac, & Weissler, 2006). Expiration preceding and following a swallow is likely a protective mechanism to help prevent aspiration by increasing subglottic pressure as the airway closes and expelling material that remains in the laryngeal vestibule post-swallow (Brodsky et al., 2010; Martin-Harris, Brodsky, Price, Michel, & Walters, 2003).

Bolus movement through the pharynx is a result of driving pressures. As the bolus is transferred to the pharynx, the base of the tongue approximates the posterior pharyngeal wall and the pharyngeal constrictors contract sequentially (Kahrilas, Logemann, Lin, & Ergun, 1992) (McConnel, 1988). These movements create driving pressures to push the bolus inferiorly. The superior to inferior contraction of the pharyngeal constrictors facilitates pharyngeal shortening which decreases the distance that the bolus must travel and reduces pharyngeal volume, which helps to increase pressure to drive the bolus through the UES (Dejaeger, Pelemans, Ponette, & Joosten, 1997; J. B. Palmer, Tanaka, & Ensrud, 2000).

In conjunction with airway protection, anterior hyolaryngeal excursion through contraction of the submental muscles, facilitates opening of the upper oesophageal sphincter (Matsuo et al., 2008). The cricopharyngeus is a narrow, semi-sphincteric muscle that connects to the lateral borders of the cricoid cartilage. It is tonically contracted at rest to prevent air passing to the stomach during passive breathing and to stop reflux from entering the pharynx (Cook, 1993). Prior to the arrival of the bolus and hyolaryngeal excursion, the cricopharyngeus muscle relaxes. The suprahyoid muscles then contract, allowing hyolaryngeal excursion, which assists with opening of the UES. Intrabolus pressure further contributes to UES opening as the bolus descends through the pharynx and passes through the UES and into the oesophagus (Jacob, Kahrilas, Logemann, Shah, & Ha, 1989; Matsuo & Palmer, 2008). As the UES opens, negative pressure in the upper oesophagus aids in pulling the bolus through the UES (McConnel, 1988).

2.2.3 Oesophageal phase

The cricopharyngeus and lower oesophageal sphincter (LES) are annular muscles that remain tonically contracted at rest to prevent the passage of air into the digestive tract and stomach contents into the pharynx. These muscles relax during vomiting, burping and swallowing to allow material to enter and exit the oesophagus. The oesophageal phase of swallowing transports the bolus through the oesophagus, from the UES to the LES. As with other phases of swallowing, there is large variability in pressure and temporal characteristics of the oesophageal phase, with the oesophageal phase of swallowing lasting between 8 and 20 seconds (Dodds, Hogan, Reid, Stewart, & Arndorfer, 1973; Logemann, 1998; A. J. Miller, 1982).

Movement of a bolus during the oesophageal phase occurs as a result of a peristaltic wave that moves from superior to inferior, creating pressure that pushes the bolus down the oesophagus and through the LES (Dornhorst, Harrison, & Pierce, 1954; Matsuo & Palmer, 2008). When in an upright position, gravity assists with oesophageal peristalsis (Matsuo & Palmer, 2008). Conscious changes in pharyngeal swallowing can affect oesophageal physiology in healthy individuals (O'Rourke et al., 2014). As an example, when performing effortful swallows, the number of non-peristaltic swallows (those in which peristalsis does not occur in the distal smooth muscle following proximal oesophageal peristalsis) is reduced and the number of peristaltic swallows is increased. Conversely, when volitionally altering timing of swallowing during the Mendelsohn manoeuvre, the number of non-peristaltic waves is increased (O'Rourke et al., 2014).

2.3 Neural control of swallowing

The complex act of swallowing requires input from multiple cortical and subcortical structures within the central nervous system (Leopold & Daniels, 2010). Cranial nerves connect the central nervous system with peripheral structures of the head and neck (Bhatnagar, 2013).

2.3.1 Motor neurons

Motor neurons are responsible for carrying motor impulses to the muscles. There are two types of motor neurons: upper motor neurons (UMN) and lower motor neurons (LMN). UMNs have two tracts that carry impulses from the cortex to the brainstem: the pyramidal tract and the extrapyramidal tract (J. A. Cichero & Murdoch, 2006). The classification of pyramidal or extrapyramidal is dependent on whether the UMNs send signals directly or indirectly to the LMNs (R. M. Miller & Britton, 2011). Neurons in the pyramidal tract travel directly from the motor cortex or precentral gyrus to the brainstem. These neurons contribute axons to the corticobulbar and corticospinal pathways and are involved in conscious, skilled movements (R. M. Miller & Britton, 2011). The extrapyramidal tract contains neurons that synapse with other structures during their course from motor cortex to the brainstem. UMNs in the extrapyramidal tract influence the LMNs that are responsible for autonomous actions (R. M. Miller & Britton, 2011). UMNs can be further subdivided dependent on the path that they take. The corticospinal tract originates at the cortex and terminates at the spinal cord.

The corticobulbar tract travels between the cortex and the medulla (Fuller, Pimentel, & Peregoy, 2012).

Damage to UMNs may result in muscle spasticity and altered reflexes, thought to be due to reduced inhibitory signals (Bhatnagar, 2013; Clark, 2003). Spasticity is characterised by a hyperactive stretch reflex. It results in an increase in muscle tone, clonus and spasms, and can be painful (Stevenson & Playford, 2016). UMN of the corticobulbar system may synapse to either ipsilateral or contralateral nuclei as decussation may occur at the pyramids. Because of this pattern of decussation, most muscles of deglutition are bilaterally innervated, providing an additional safety mechanism following neural lesion. However, muscles of the lower 2/3 of the face only receive input from UMNs that arise from the contralateral side of the cortex.

Bulbar LMNs continue from the motor nuclei of the brainstem to the bulbar muscles (J. A. Cichero & Murdoch, 2006). A muscle fibre is innervated by one motor neuron; however, each motor neuron may innervate multiple muscle fibres, thus damage to a motor neuron will result in a disruption of signal to the muscle fibres innervated by that motor neuron (Clark, 2003). LMN damage may result in ipsilateral muscle fasciculations, followed by atrophy due to disuse and flaccidity due to the lack of efferent motor impulses to the muscle fibres (Bhatnagar, 2013; Clark, 2003).

2.3.2 Cranial nerves

There are 12 bilaterally represented CNs that relay signals between the brain and various regions of the body, seven of which are involved in the process of swallowing. These are the olfactory nerves (CN I), optic nerves (CN II), trigeminal nerves (CN V), facial nerves (CN VII), glossopharyngeal nerves (CN IX), vagus nerves (CN X) and hypoglossal nerves (CN XII).

CN I and CN II are involved during the pre-oral phase of swallowing. They contain only sensory fibres that are stimulated by the smell and sight of food respectively. CN I delivers information from the neuroepithelial olfactory cells in the nasal mucosa to the primary olfactory area. CN II delivers afferent information from the retina to the primary visual cortex in the occipital lobe (Bhatnagar, 2013).

CN V is divided into three branches: the ophthalmic, maxillary and mandibular nerves. The ophthalmic and maxillary nerves carry only afferent information, while the mandibular nerve

is made up of both sensory and motor neurons. The principal sensory nucleus of CN V is located in the lateral aspect of the pons and the motor nucleus is located medial to the primary sensory nucleus. CN V transmits pain, temperature, tactile and proprioceptive sensory information from the face, oral cavity, nasal cavity and regions of the scalp (Bhatnagar, 2013). Sensory neurons from CN V convey information to the nucleus of the trigeminal nerve and subsequently to the nucleus tractus solitarius (NTS) if the information is related to swallowing (A. J. Miller, 2008). There are multiple motor branches of CN V. The first of these is the masticatory branch, which as the name suggests, innervates the muscles of mastication (temporalis, masseters and medial and lateral pterygoid muscles). The mylohyoid branch innervates the mylohyoid and the anterior belly of digastric muscles. The final motor branch of CN V is the mandibular branch; this innervates the tensor veli palatini muscles, which are involved in raising the soft palate to achieve velopharyngeal closure during swallowing.

CN VII provides motor innervation to the posterior belly of digastric and the stylohyoid muscles, which are necessary for superior hyolaryngeal excursion. CN VII also innervates muscles of the face, including the buccinators and orbicularis oris, which are integral for bolus containment and preparation during the oral phase of swallowing. Parasympathetic innervation by CN VII to the sublingual and submandibular glands, contributes to saliva production during pre-oral and oral phases (Bhatnagar, 2013; Koch, Ferrazzi, Busatto, Ventura, & Palmer, 2017). Afferent fibres of CN VII convey sensory information regarding the anterior two-thirds of the tongue and the nasopharynx.

Motor neurons of CN IX innervate the stylopharyngeus muscles, which contribute to elevation of the hyoid and larynx during swallowing (Mistry & Hamdy, 2008). The inferior salivatory nuclei provide parasympathetic information to the largest salivary gland, the parotid gland. Afferent fibres provide taste and general sensory information from the posterior one third of the tongue (Vilensky, Robertson, & Suarez-Quian, 2015). CN IX also provides the afferent input for the gag reflex, a protective reflex that occurs in response to tactile sensory stimulation of the pharyngeal wall, posterior tongue, tonsils or faucial pillars. The gag motor response involves contraction and shortening of the oropharynx and is innervated by the pharyngeal plexus (PP), discussed below (Campbell & DeJong, 2013; Mistry & Hamdy, 2008).

CN X is the longest cranial nerve and is made up of both afferent and efferent fibres (Campbell & DeJong, 2013). As well as swallowing, CN X also plays a role in speech, respiratory, cardiovascular and gastrointestinal function (Vilensky et al., 2015). Three of the ten branches of CN X are involved in the pharyngeal phase of swallowing. These are the pharyngeal nerve, superior laryngeal nerve (SLN) and recurrent laryngeal nerve (RLN). The pharyngeal nerve is the principle motor nerve; it innervates the pharyngeal constrictors and muscles of the soft palate, except the tensor veli palatini (innervated by CN V) (Fuller et al., 2012). There are two branches of the SLN, the internal and external branches. The internal branch of the SLN carries sensory information from the tongue, epiglottis and the larynx above the vocal folds. The external branch of the SLN provides fibres to the PP and innervates the inferior pharyngeal constrictors and the cricothyroid muscles (Kierner, Aigner, & Burian, 1998; Sun & Chang, 1991). Stimulation of the SLN results in swallowing, and anesthetisation of the SLN increases risk of penetration and aspiration. The RLN is the primary efferent nerve for all laryngeal muscles, except the cricothyroid, and is therefore, important for airway protection during swallowing (Vilensky et al., 2015). The RLN also transmits sensory information from the larynx below the vocal folds and superior oesophagus (Fuller et al., 2012).

The PP is made up of fibres from both CN IX and CN X; however, the contributions of each of these nerves are not fully understood (Gutierrez et al., 2020). The PP innervates the levator veli palatini muscles, which contribute to elevation the soft palate, to close off the nasopharynx during swallowing. The palatoglossus muscles are also innervated by PP; these muscles achieve posterior glossopalatal approximation during bolus preparation. The PP is integral in base of tongue retraction during swallowing as it innervates the glossopharyngeus muscles. The salpingopharyngeus, palatopharyngeus and the pharyngeal constrictor muscles are also innervated by PP (Gutierrez et al., 2020). Finally, afferent fibres of the PP convey sensory information from the oropharynx and hypopharynx, which is important for detecting pharyngeal residue. Innervation of the cricopharyngeus muscle is controversial in the literature. It has been proposed that the PP, RLN and the external branch of the SLN contribute to innervation of the cricopharyngeus (Gutierrez et al., 2020; Hammond, Davenport, Hutchison, & Otto, 1997; Sasaki, Sims, Kim, & Czibulka, 1999; Uludag, Aygun, & Isgor, 2017).

CN XII innervates all of the intrinsic and extrinsic muscles of the tongue, except the glossopharyngeus and palatoglossus muscles (innervated by PP) (Fuller et al., 2012). The intrinsic lingual muscles alter the tongue's shape and the extrinsic lingual muscles change the position of the tongue within the oral cavity and allow for lingual protrusion and retraction (Daniels & Huckabee, 2014; Koch et al., 2017).

There are discrepancies in the literature regarding the fibres that make up the ansa cervicalis (AC). These discrepancies likely arise due to the variability of the nerve's course and significant differences between individuals in the arrangement of the contributing roots and patterns of branches (Chhetri & Berke, 1997). The AC has two roots: the superior root and the inferior root. The superior root is made up of fibres from CN XII, and the first and second cervical nerves (C1 & C2) (Banneheka, 2008). The inferior root is comprised of branches from the first four cervical nerves (C1-C4); however the branches and the course of the inferior root were found to be highly variable between individuals (Banneheka, 2008). The AC innervates the geniohyoid muscles, which contribute to hyolaryngeal excursion and the anterior strap muscles, which elevate the larynx and epiglottis (D. J. Curtis, Braham, Karr, Holborow, & Worman, 1988).

2.3.3 Brainstem control of swallowing

The motor nuclei of many of the CNs that are essential for swallowing are found within the brainstem. The pons houses the sensory nucleus of CN V and the motor nuclei of CN V and CN VII. The motor nucleus of CN XII, the nucleus tractus solitarius (NTS) and the nucleus ambiguous (NA) are located in the medulla. A central pattern generator (CPG) within the brainstem provides the basic motor plan for the sequential, rhythmic patterns of swallowing, evidenced by the capacity to induce a replicable swallowing motor pattern with electrical current in decerebrate animals (Jean, 2001; Oku, Tanaka, & Ezure, 1994).

The regions that represent the swallowing CPG are the dorsal swallowing group and the ventral swallowing group. The dorsal swallowing group consists of the NTS and surrounding regions. The primary sensory nuclei of CN VII, CN IX and CN X are located in the NTS. Peripheral nerves associated with these nuclei carry sensory information directly to the NTS via afferent pathways. The NTS also receives information that is related to swallowing from the cortex and trigeminal sensory nucleus (located in the pons) (Ertekin, 2011). The neurons within the dorsal swallowing region are responsible for driving the initiation of pharyngeal

swallowing, sequencing of swallowing events and adaptation of swallowing in response to bolus characteristics. Once information is received by the dorsal swallowing group, it is integrated into a motor plan and sent to the ventral swallowing group via interneurons.

The ventral region of the swallowing CPG includes the NA and its surrounding area. The primary motor nuclei of CN IX and CN X are located in the NA. The NA is organised myotopically, corresponding to the rostral-caudal pattern of motor neurons that make up the pharynx, larynx and oesophagus. The NA and surrounding reticular formations also have strong connections to the trigeminal and hypoglossal motor neurons, aiding timely and efficient swallowing (Amri, Car, & Roman, 1990; Holstege, Kuypers, & Dekker, 1977; Jean, Amri, & Calas, 1983). Efferent neurons within the motor branches of cranial nerves transmit signals from the NA to the peripheral muscles.

2.3.4 Cortical control of swallowing

Although swallowing can be initiated via stimulation to the brainstem in decerebrate animals, cortical input is necessary for modulation of the basic motor plan in response to sensory information and cognitive input. Lesion studies have demonstrated that a unilateral cortical lesion can result in dysphagia, highlighting the importance of this region in safe and efficient swallowing (Daniels & Foundas, 1999). Historically, the pharyngeal phase of swallowing was considered reflexive, as it is not possible to terminate the sequence of events once they have begun. However, unlike a true reflex, modification of swallowing can occur in response to sensory feedback and/or volitional control. The cortex is essential in the integration of sensory information from the bolus and the volitional adaptation of swallowing (Peck et al., 2010). Volitional manipulation of pharyngeal swallowing can occur through increasing or decreasing effort (Doeltgen, Ong, Scholten, Cock, & Omari, 2017; Hind, Nicosia, Roecker, Carnes, & Robbins, 2001; Hiss & Huckabee, 2005; Huckabee, Butler, Barclay, & Jit, 2005; Molfenter, Hsu, Lu, & Lazarus, 2018) or prolonging aspects of a swallow such as laryngeal vestibule closure or UES opening (Azola, Sunday, & Humbert, 2017; Doeltgen et al., 2017; Inamoto et al., 2018; Kahrilas, Logemann, Krugler, & Flanagan, 1991; Macrae, Anderson, Taylor-Kamara, & Humbert, 2014).

Onset of cortical activation occurs two seconds prior to swallowing onset and continues up to 23 seconds after swallowing, indicating that the cortex is involved from the oral to the oesophageal phase (Huckabee, Deecke, Cannito, Gould, & Mayr, 2003; Kamarunas,

Mulheren, Palmore, & Ludlow, 2017). Cortical activation has been investigated through electroencephalography (EEG) (Huckabee et al., 2003), functional magnetic resonance imaging (fMRI) (Malandraki, Sutton, Perlman, Karampinos, & Conway, 2009; Martin, Goodyear, Gati, & Menon, 2001; Martin et al., 2004) and functional near-infrared spectroscopy (fNIRS) (Kamarunas et al., 2017). Cortical areas that are frequently reported to be activated during swallowing are the primary sensorimotor cortex, premotor cortex, anterior cingulate gyrus, supplementary motor areas, insula and frontal operculum (Malandraki et al., 2009; Michou & Hamdy, 2009).

Sensory information from the bolus is integrated by structures in the cortex to adapt the motor response (Miller, 1999). This may include alterations to the strength or duration of the swallowing response due to specific bolus characteristics or volitional control. This allows safe ingestion of boluses that are different sizes, consistencies, and temperatures (Daniels & Huckabee, 2014). Neural control of voluntary swallowing is organised into parallel circuits (Mosier & Bereznaya, 2001). These circuits connect the sensorimotor, premotor and parietal areas with the cerebellum and insula. It is believed that this organisation facilitates planning and implementation of the complex swallowing motor events (Mosier & Bereznaya, 2001). During swallowing, neural activation initially occurs in the premotor cortex, supplementary motor area and bilateral thalamus, followed by the primary sensorimotor cortex, the posterior insula and cerebellum, and finally the pons in the brainstem (Mihai et al., 2014). Additional activation in the caudal anterior cingulate cortex has been observed in volitional swallowing (Martin et al., 2001).

Bilateral cortical activation occurs during swallowing; however, the presence of hemispheric dominance is debated in the literature, with currently inconclusive results. There is literature that argues that the right hemisphere is dominant for the pharyngeal phase of swallowing, while the left hemisphere is dominant for the oral phase (Robbins & Levine, 1988; Robbins, Levine, Maser, Rosenbek, & Kempster, 1993; Teismann, Dziewas, Steinstraeter, & Pantev, 2009). Whereas other research argues that although hemispheric dominance may be present at the individual level, there is no population wide dominant hemisphere for the pharyngeal phase of swallowing (Hamdy et al., 1997; Hamdy et al., 1996; Hamdy et al., 1999; Kamarunas et al., 2017; Mosier, Liu, Maldjian, Shah, & Modi, 1999; Vasant et al., 2014).

3. Motor Neurone Disease

Motor neurone diseases are a group of diseases that are predominantly caused by the degeneration of motor neurons, resulting in progressive weakness. Amyotrophic Lateral Sclerosis (ALS) is the most common form of Motor Neurone Disease (MND), characterised by degeneration of both UMN and LMN in the primary motor cortex, brainstem and spinal cord (Brown & Al-Chalabi, 2017; Rowland & Shneider, 2001). Primary lateral sclerosis is a less common variant of MND, in which degeneration occurs only in the UMN, resulting in spasticity, emotional lability, weakness and pathological reflexes (Pringle et al., 1992). There are also three LMN variants: progressive bulbar palsy, in which degeneration occurs to only the bulbar LMN, progressive muscular atrophy, in which only spinal LMN are affected, and spinal bulbar muscular atrophy (Kennedy's disease), which is a genetic disease that affects the bulbar and spinal LMN (Kennedy, Alter, & Sung, 1998). As ALS is the most common form of MND, the terms ALS and MND are often used interchangeably. For the purpose of this thesis, the term MND will be used to describe all types of motor neurone diseases, including ALS.

The global incidence of MND is reported to be between 1.68 and 2.08 per 100,000 per year (A Chio et al., 2013; Marin et al., 2017). MND is most common in men and those aged between 60 and 69 (Mehta, 2015; Valadi, 2015). The prevalence of MND is approximately 5.40 per 100,000 people (A Chio et al., 2013). Murphy, Quinn, Young, Parkin, and Taylor (2008) reported that in New Zealand (NZ), the incidence of MND is increasing, changing from 1.6 to 3.3 people per 100,000 between 1985 and 2006. However, this study did not account for the aging population. When the aging population was considered, mortality rate of MND in NZ did not appear to increase over time, instead remaining stable at approximately 2.8 per 100,000 (Cao, Chancellor, Charleston, Dragunow, & Scotter, 2018). Although the incidence in NZ is greater than the global incidence, the age adjusted incidence in the indigenous Māori population in NZ is only 1.21 per 100,000 (Cao et al., 2018). These differences could be a result of differences in genetic susceptibility, environmental factors or reduced interaction with health care in the Māori population.

The cause of MND is unknown; however, it is believed to be a result of interplay between genetic susceptibility and environmental factors (Oskarsson, Horton, & Mitsumoto, 2015). Five to ten percent of cases of MND have been linked to genetics, often dominantly inherited

autosomal mutations (Brown & Al-Chalabi, 2017; Saberi, Stauffer, Schulte, & Ravits, 2015; Scotter, 2015). The number of known genetic mutations leading to MND has been increasing since the 1993 discovery of the SOD1 gene, which accounts for 20% of familial MND cases (Rosen et al., 1993; Saberi et al., 2015). There are now more than 25 identified genes that are associated with familial and/or sporadic MND (Brown & Al-Chalabi, 2017). Other common genetic mutations that lead to susceptibility for MND include mutations to the TDP-43 gene, responsible for the TAR-DNA binding protein, and the FUS gene, responsible for the FUS-RNA binding protein (Kiernan et al., 2011). Although largely speculative, it is believed that MND develops when an individual who is genetically predisposed to the condition is exposed to certain environmental factors (Al-Chalabi & Hardiman, 2013). Possible contributing environmental factors include head trauma (Armon & Nelson, 2012), heavy metal exposure (Portaro, Naro, Giorgianni, Mazzon, & Calabrò, 2019), and tobacco smoking (De Jong et al., 2012). Military service has also been observed to be correlated with high rates of MND; however, causal factors associated with service have not been identified (Beard & Kamel, 2015; Tai et al., 2017; Weisskopf et al., 2005).

The defining neuropathology of MND is the degeneration of motor neurons. Motor neuron degeneration often occurs in the motor cortex, nuclei in the lower brainstem and the anterior horns of the spinal cord (Hohenfeld, Werner, & Reetz, 2018; J. P. Taylor, Brown, & Cleveland, 2016; Williams & Windebank, 1991). The neurons that innervate the extraocular muscles and the bladder are usually spared until late in disease progression (Brown & Al-Chalabi, 2017). The exact pathogenesis of MND is unknown, but there are several cellular mechanisms and processes that are believed to be involved. These include protein aggregation and mis-folding, inflammation, glutamate excitotoxicity, generation of free radicals, oxidative stress and mitochondrial dysfunction (J. P. Taylor et al., 2016).

There is a large amount of variation in symptom presentation and progression between individuals with MND (Renton, Chiò, & Traynor, 2014; Swinnen & Robberecht, 2014). In 75% of patients, the initial symptoms involve the upper or lower limbs. Approximately 25% of patients present with bulbar symptoms and only a small number present with respiratory symptoms as the initial symptom (Wijesekera & Leigh, 2009; Zoccolella et al., 2006). However, in most cases, symptoms spread to include spinal, bulbar and respiratory muscles by the end stages of the disease. Demographic factors can help to predict disease onset type.

For example, females and older patients (diagnosed after 75) are more likely to present with bulbar onset MND than males and younger patients (Zoccolella et al., 2006).

Due to the large amount of symptom variation between patients, and the lack of a biological diagnostic marker for MND, providing a definitive diagnosis is challenging, and rates of misdiagnosis are high (Brooks, Miller, Swash, & Munsat, 2000; Househam & Swash, 2000). Time from symptom onset to diagnosis of MND is, on average, 11 months, with an increase in delay for those who are initially misdiagnosed (Cellura, Spataro, Taiello, & La Bella, 2012). Research investigating possible biomarkers for MND is ongoing. Possible methods of facilitating earlier diagnosis include the use of ultrasound to detect fasciculations (Misawa et al., 2011) or electrical impedance myography to detect changes in muscle composition (Alix et al., 2020). Increasing the speed of diagnosis and diagnostic accuracy is crucial for patients with MND, as earlier intervention may increase life expectancy through earlier implementation of treatments.

As a result of rapid motor decline following initial symptoms, half of the patients diagnosed with MND do not survive the first 30 months from the time of symptom onset (Kiernan et al., 2011). However, there is a large amount of between patient variability in disease progression, and approximately 12% of patients survive longer than 10 years from the time of diagnosis (Pupillo, Messina, Logroscino, Beghi, & Group, 2014). Older age at symptom onset and bulbar onset of symptoms have been demonstrated to be independent factors that result in a poorer prognosis (A. Chio et al., 2009; A. Chiò et al., 2002; Millul et al., 2005).

3.1 Cognition in MND

Traditionally, there was the belief that, for patients with MND, neural degeneration was restricted to the motor neurons, and therefore, cognition was spared. However, approximately 40 - 51% of patients with MND have some degree of cognitive impairment, and 10 – 15% meet the criteria for frontotemporal dementia (Gordon et al., 2011; Ringholz et al., 2005). In patients with MND, cognitive impairment is associated with changes to the temporal and frontal lobes (Abrahams et al., 2004). Therefore, impairments include deficits in executive function and working memory, which extend to altered language and social cognition (Goldstein & Abrahams, 2013). Interestingly, of those with frontotemporal dementia and MND, there is an overrepresentation of patients with corticobulbar onset MND compared to the corticospinal type (Lomen-Hoerth et al., 2003).

Survival time in patients with MND who have associated frontal impairment has been shown to be shorter than for patients with normal cognitive functioning (R. G. Miller et al., 2009; Olney et al., 2005). Reduced acceptance of medical interventions such as percutaneous endoscopic gastroscopy (PEG) feeding and non-invasive ventilation (NIV) has been demonstrated in this population this subgroup of patients (Achi & Rudnicki, 2012), which may contribute to length of survival.

3.2 Dysphagia in MND

Over the course of MND, dysphagia presents in 86% to 98% of patients with the corticobulbar subtype, and in approximately 73% of patients with the corticospinal subtype (A. Chen & Garrett, 2005; Kühnlein et al., 2008; Onesti et al., 2017). Dysphagia in MND is progressive, and, as with the disease itself, the rate of progression is highly variable between patients (Higo, Tayama, & Nito, 2004). Dysphagia is often underreported by patients with MND, likely due to gradual adaptation to progressive decline (Onesti et al., 2017). With high levels of individual variability, risk of underreporting and the progressive nature of dysphagia, frequent assessment is necessary (Garand, Schwertner, Chen, & Pearson, 2018).

Any and all phases of swallowing can be affected by MND (Kühnlein et al., 2008), resulting in negative impacts on both quality and duration of life (Paris et al., 2013). Spastic and flaccid characteristics can be present in bulbar muscles, as demonstrated by the common presentation of mixed spastic-flaccid dysarthria (Darley, Aronson, & Brown, 1969). Therefore, although it has not been directly investigated, it is feasible to speculate that characteristics of both flaccidity and spasticity may contribute to aspects of dysphagia.

3.2.1 Oral phase dysphagia

The oral phase is often the first phase of swallowing to be affected by MND (Briani et al., 1998; Higo, Tayama, Watanabe, & Nitou, 2002; Hillel & Miller, 1989; Kawai et al., 2003; Ruoppolo et al., 2013). Oral phase dysphagia is predominantly due to degeneration of motor neurons associated with CN XII. This can result in atrophy, weakness and fasciculation of the tongue (Britton, Cleary, & Miller, 2013; Kawai et al., 2003). Changes in the strength and range of motion of lingual muscles often lead to oral residue and decreased masticatory efficiency, increasing the time and effort necessary to consume a meal (D'Ottaviano, Linhares Filho, de Andrade, Alves, & Rocha, 2013; Fattori et al., 2006; Jani & Gore, 2016; Ruoppolo et al., 2013). Tongue speed and range of motion have also been correlated with

swallowing safety when drinking thin liquids and tongue strength associated with swallowing safety when consuming puree (B. J. Perry, Stipancic, Martino, Plowman, & Green, 2020). Tongue thickness measured by ultrasound is correlated with oral transit time and body mass index (BMI) in patients with MND, but not in healthy controls, demonstrating that oral phase dysphagia is associated with poor nutritional outcomes (Nakamori et al., 2015). However, it is important to consider that atrophy of muscles over disease progression will contribute to a decrease in BMI so it cannot be assumed that the correlation between tongue thickness and BMI is causative.

Muscles of mastication are also impacted by MND, resulting in reduced bite strength. Interestingly, despite the reduction in bite strength, self-injury due to biting oneself during mastication is increased in patients with bulbar onset MND compared to controls. This may indicate disruption to the sensory feedback loop having a greater impact than reduced strength (Riera-Punet, Martinez-Gomis, Paipa, Povedano, & Peraire, 2018; Riera-Punet, Martinez-Gomis, Willaert, Povedano, & Peraire, 2018). Anterior loss of a bolus or saliva is common due to poor labial seal and decreased frequency and efficiency swallowing saliva at rest (Dand & Sakel, 2010). In addition to drooling, patients with MND report that the excess saliva can hinder speech, that it has negative social implications and that it can cause coughing, likely due to aspiration (McGeachan, Hobson, Shaw, & McDermott, 2015).

An additional aspect of oral phase dysphagia is reduced glossopalatal approximation (Higo et al., 2004; Higo et al., 2002; Leder, Novella, & Patwa, 2004; Walshe, 2014). This biomechanical impairment has been demonstrated to result in premature spillage of a bolus into the pharynx, which can contribute to airway invasion. The depth of pre-swallow pharyngeal pooling has been demonstrated to increase with disease progression (Leder et al., 2004).

3.2.2 Pharyngeal phase dysphagia

Due to the complexity of pharyngeal swallowing, there are many aspects that may be affected by MND. Inefficient swallowing, demonstrated by post-swallow residue, is often one of the earliest changes to pharyngeal stage (D'Ottaviano et al., 2013; Fattori et al., 2006; Higo et al., 2004; Teismann et al., 2011; Waito et al., 2020; Waito, Tabor-Gray, Steele, & Plowman, 2018; Walshe, 2014; Wright & Jordan, 1997). Swallowing inefficiency can contribute to fatigue, prolonged meals and reduced quality of life (Paris et al., 2013; Tabor, Gaziano,

Watts, Robison, & Plowman, 2016). The presence of pharyngeal residue is likely a result of reduction in pharyngeal pressure generation due to reduced base of tongue to posterior pharyngeal wall contact and reduced pharyngeal constriction (Goeleven, Robberecht, Sonies, Carbonez, & Dejaeger, 2006; Waito et al., 2018). The levator veli palatini muscles that elevate the soft palate and separate the oropharynx from the nasopharynx during swallowing may become weak as a result of the disease (J. Tomik et al., 2017). This is demonstrated by hypernasal speech, a common presentation in individuals with MND (B. Tomik & Guiloff, 2010). Decreased palatal elevation may be a contributing factor to reductions in pharyngeal pressure. The decline in pharyngeal pressure generation during swallowing is progressive over time, often beginning in the oropharynx and expanding to include hypo-pharyngeal weakness approximately one year post-onset of bulbar symptoms (Higo et al., 2004; J. Tomik et al., 2017). Post-swallow residue increases the risk for post-swallow airway invasion (Goeleven et al., 2006). To compensate for inefficiency and reduce the amount of residue, patients often spontaneously reduce the size of the bolus that they ingest, taking multiple swallows to complete one mouthful (Tamburrini et al., 2010; Waito et al., 2018).

MND can result in reduced speed and distance of anterior hyolaryngeal excursion, likely indicating dysfunction of the submental muscles (Waito, 2019). Further, during swallowing, duration of submental muscle activity is increased compared to healthy controls; however, this does not result in prolonged hyolaryngeal excursion (Ertekin et al., 2000). Impaired submental muscle activity can lead to inadequate and delayed epiglottic deflection, which can contribute to airway invasion (Waito, 2019; Waito et al., 2020). Patients with MND do not demonstrate differences in hyoid excursion between different liquid consistencies, indicating reduced ability to spontaneously adapt swallowing in response to bolus properties (Waito, 2019). This may indicate that patients are compensating for dysfunction by constantly swallowing with their maximal power output, resulting in an inability for greater muscle recruitment and structural displacement in response to thicker boluses.

UES opening is preserved in approximately two thirds of patients and has been shown to be well maintained until the late stages of the disease (Higo et al., 2004). However, in one third of patients, opening of the UES is delayed in relation to onset of submental muscle activity, the duration of opening is reduced and cricopharyngeal motor bursts occur within the period of UES opening (Ertekin et al., 2000). Reduced opening of the UES suggests hypertonicity of the cricopharyngeus muscle due to UMN damage or weakness of the submental muscles

resulting in inadequate laryngeal excursion (Fattori et al., 2006; J. Tomik et al., 2017). A reduction in the time and extent of UES opening can lead to pyriform sinus residue and airway invasion during or after swallowing.

3.2.3 Oesophageal phase dysphagia

Oesophageal phase dysphagia has not been as thoroughly investigated as oropharyngeal dysphagia, likely because the level of impairment is not as significant (Briani et al., 1998). However, it has been reported that patients with MND experience changes to oesophageal peristalsis (Briani et al., 1998; J. Tomik, Sowula, Ceranowicz, Dworak, & Stolcman, 2020) and impaired function of the lower oesophageal sphincter in a small percentage of patients (Briani et al., 1998).

3.2.4 Respiratory contribution to dysphagia

In a small group of patients, respiratory weakness is the initial symptom of MND, and by the late stages of the disease, almost all patients will suffer from respiratory insufficiency (Heffernan et al., 2009). All muscles of respiration can be impacted, including the intercostal muscles, the diaphragm and the accessory muscles. Symptoms of respiratory weakness may include fatigue secondary to awakening during the night, hypercapnia, weak voice, weak cough and dysphagia (Hardiman, 2011; Morelot-Panzini, Bruneteau, & Gonzalez-Bermejo, 2019). Percentage of baseline forced vital capacity (FVC) is the most common method of monitoring decline in pulmonary function (Melo et al., 1999). It has been shown to be a significant predictor of disease progression and survival time (Czaplinski, Yen, & Appel, 2006).

Respiratory weakness can contribute to dysphagia as it affects respiratory swallow coordination and supraglottic pressure during swallowing (Gross et al., 2003; Gross, Atwood Jr, Ross, Olszewski, & Eichhorn, 2009; Gross et al., 2006). Individuals with MND have an increased duration of swallowing apnoea when compared to healthy controls (Nozaki et al., 2008). This means that patients are more likely to inspire after swallowing, which could lead to aspiration (Hadjikoutis & Wiles, 2001; Nozaki et al., 2008). Weak respiratory muscles may also decrease an individual's ability to produce an effective cough response, resulting in an inability to clear aspirated material. Plowman, Watts, Robison, et al. (2016) demonstrated that patients whose swallowing was unsafe (PAS $\geq$ 3), had a lower cough volume acceleration, lower peak expiratory flow rate and greater time to reach peak flow during

voluntary cough than patients in the safe swallowing group. This relationship may be due to a concomitant reduction in strength of both of these subsystems or could be more directly related, with a reduction in respiratory muscle strength leading to poor respiratory swallow coordination and reduced ability to clear aspirate through coughing.

The motor pattern associated with coughing is altered in patients with MND compared to healthy individuals (Tabor-Gray, Gallestagui, Vasilopoulos, & Plowman, 2019). Velocity of vocal fold adduction during the expulsive phase of coughing is reduced, which may contribute to reduced cough effectiveness (Britton et al., 2014). During voluntary and reflexive coughing, patients demonstrate a longer inspiratory phase duration and a longer time to produce peak expiratory velocity, which results in reduced peak cough flow, indicating impairment in muscles of inspiration and expiration (Tabor-Gray et al., 2019; Tabor-Gray, Vasilopoulos, Wheeler-Hegland, Wymer, & Plowman, 2020). This slower and weaker cough response is likely to be less effective at clearing aspirated material and pulmonary secretions, and a reduced spike in peak flow during cough has been demonstrated to be associated with increased mortality (Chaudri, Liu, Hubbard, Jefferson, & Kinnear, 2002). Importantly, when assessing cough strength in patients with MND, cough volume acceleration and peak expiratory flow rate have been shown to be greater during voluntary coughing than reflexive coughing. (Tabor-Gray, Vasilopoulos, & Plowman, 2020). If used as a clinical assessment voluntary coughing may overestimate a patient's true reflexive function. This is likely due to the fact that a greater lung volume results in a greater peak cough flow. Voluntary coughs are able to be produced at a full lung volume, however an individual has less control over this during reflexive coughing as it occurs at the point of sensory input (J. A. Smith et al., 2012). Sensory changes associated with reflexive coughing are discussed below.

3.2.5 Sensory changes to swallowing in MND

Historically, it was believed that MND solely affected motor neurons; however, there is emerging evidence that sensation can also be impacted over the course of the disease. Up to 20% of patients report sensory symptoms, including numbness, decreased sensation to temperature, tingling and neuropathic pain (Tao, Wei, & Wu, 2018). Nerve conduction studies and biopsies have demonstrated that disruption to the sensory mechanism in spinal nerves is common in patients with MND (Hammad, Silva, Glass, Sladky, & Benatar, 2007; Isak et al., 2016; Nolano et al., 2017; Pugdahl et al., 2007; Weis et al., 2011). Evidence of sensory impairment to bulbar regions includes altered reflexes, reduced taste, reduced smell

and the presence of odynophagia (Hawkes, Shephard, Geddes, Body, & Martin, 1998; Jesus et al., 2012; Karen Fontes Luchesi, Kitamura, & Mourão, 2014; Pelletier, Abou-Zeid, Bartoshuk, & Rudnicki, 2013).

The laryngeal adduction reflex (LAR) is a rapid closure of the vocal folds in response to sensory stimulation of the larynx. The absence of a reflexive response is a predictor of penetration and aspiration during swallowing (Aviv et al., 2002; Domer, Kuhn, & Belafsky, 2013). To investigate changes in pharyngeal sensitivity, Amin, Harris, Cassel, Grimes, and Heiman-Patterson (2006) recruited 27 patients, 22 of which tolerated the assessment. Patients underwent flexible endoscopic evaluation of swallowing with sensory testing (FEESST). Sensory threshold was tested by applying varying intensities of air pulses to the arytenoids and assessing a patient's response. Approximately half of the patients with MND who tolerated the assessment demonstrated a sensory threshold below what is considered normal. This was the first study to identify laryngeal sensory changes in patients with MND.

Another swallowing related reflex that can be impaired due to changes in sensation is the cough response to aspiration. A high incidence of silent aspiration on VFSS has been reported (Goeleven et al., 2006; Lo Re et al., 2007), indicating that a reduction in laryngeal sensation is common in individuals with this disease. Cough response was reported to be impaired in 10 of 49 patients, as measured by FEES; however, the precise method for detecting impairment was not specified (Ruoppolo et al., 2013). Further research investigating reflexive cough in response to nebulised capsaicin has demonstrated an increase in cough sensitivity in patients with no evidence of aspiration when compared to healthy controls and a decrease in sensitivity in those who demonstrated silent aspiration on VFSS (Tabor-Gray, Vasilopoulos, Wheeler-Hegland, et al., 2020). The observed increase in cough sensitivity may be due to UMN degeneration resulting in hyperreflexia. Alternatively, as the scale used was a perceptive scale of a participants urge to cough, those in the patient group may have rated higher due to heightened awareness and fear associated with the need to cough. Conversely, those with silent aspiration demonstrated a blunted sensorimotor response. This indicates a progressive change in upper airway sensitivity, potentially due to degradation of afferent cough receptors or desensitisation as a result of chronic aspiration.

3.2.6 Effects of dysphagia in MND

Dysphagia can lead to negative health outcomes such as malnutrition and aspiration pneumonia, which can result in death. Aspiration pneumonia can contribute to respiratory failure, which has been reported as the cause of death in between 65.5% (Yang et al., 2011) and 97% (Burkhardt, Neuwirth, Sommacal, Andersen, & Weber, 2017) of patients with MND. The large variation in cause of death between these studies may be due to the date of publication and differences in health care between the locations. In the Chinese cohort, only 1.4% of patients received nutrition through a PEG tube found that 26% of patients died from nutritional causes (Yang et al., 2011). In the Swiss population evaluated by Burkhardt et al. (2017), 65% of patients received nutrition through a PEG tube and no patients were reported to die due to nutritional causes. Post-mortem evaluations identified that aspiration pneumonia was the direct cause of death in 11% to 31% of patients (Burkhardt et al., 2017; Corcia et al., 2008; Kurian, Forbes, Colville, & Swingler, 2009). One possible explanation for the large variation in mortality as a result of aspiration pneumonia may be the authors' definition of aspiration pneumonia as a cause of death. Burkhardt et al. (2017), who reported the greatest incidence of aspiration pneumonia as cause of death, defined aspiration pneumonia as "…the presence of putrid pneumonia intermixed with aspiration material, squamous epithelium (from the oesophagus and oropharynx) and bacteria, as well as characteristic brownish coagulation necrosis and haemorrhages of lung tissue as a reaction of gastric acid." (p. 3). The higher rate of aspiration pneumonia identified by this study may be due to more extensive testing for the presence of aspiration compared to other research, which did not define aspiration pneumonia and may, therefore, have attributed death to the more general bronchopneumonia.

Patients with MND are highly susceptible to malnutrition as they may have an increased resting metabolic rate, dysphagia, difficulty self-feeding, food avoidance behaviours and reduced appetite (Bouteloup et al., 2009; Dupuis, Pradat, Ludolph, & Loeffler, 2011; Kühnlein et al., 2008; Limousin et al., 2010; Muscaritoli et al., 2012; Ngo, Steyn, & McCombe, 2014). Approximately 60% of patients demonstrate a 10% increase in resting energy expenditure. The reason for this is unknown but it is theorised that hypermetabolism may be either a consequence of increased energy demand of the atrophying muscles or increased energy expended when fighting infection (Claude Desport, 2000). Malnutrition is a significant risk factor that has been reported to result in up to 26% of deaths (A Chio et al.,

2013; Yang et al., 2011), and increases the risk of mortality by 7.7 times when compared to an individual who is not malnourished (Desport et al., 1999).

Not only does dysphagia increase the risk of pneumonia and malnutrition, it also has a negative effect on the quality of life of patients with both spinal and bulbar onset MND (da Costa Franceschini & Mourao, 2015; Korner et al., 2013; Paris et al., 2013; Tabor et al., 2016). Swallowing and respiratory symptoms were the only symptoms measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R) that significantly correlated with self-rated depression (Hillemacher et al., 2004). Further research also documents correlations between the presence of dysphagia and reduced quality of life as measured by the Swal-QOL (Paris et al., 2013; Tabor et al., 2016). When compared to patients who did not have dysphagia, dysphagic patients had significantly higher impairment scores on the subscales of burden, food selection, eating duration, eating desire, fear, communication, mental health and social aspects of eating (Paris et al., 2013). This demonstrates the wide-reaching effects that dysphagia has on quality of life. Patients with spinal onset MND demonstrate the most impairment in the domains of eating duration and social function of the Swal-QOL, with 70% of patients in this group avoiding eating socially (da Costa Franceschini & Mourao, 2015). This likely reflects the difficulty using the upper limbs to move food to the mouth in patients with spinal symptoms.

4. Routine management

There is no cure for MND; therefore, symptom management is the focus of medical professionals. The symptoms associated with MND are heterogeneous and management requires a variety of behavioural, surgical and medicinal approaches.

4.1 Medicinal management of MND

Medical intervention may slow the progression of MND or reduce symptoms for a period of time. Riluzole is the only publicly funded drug available in NZ. It is used to slow the progression of symptoms and prolong life, albeit by only approximately two to four months (R. G. Miller, Mitchell, & Moore, 2012; Traynor, Alexander, Corr, Frost, & Hardiman, 2003). A Cochrane review of the literature identified three studies that investigated the effect of Riluzole on bulbar function (R. G. Miller et al., 2012). None of these studies demonstrated significant improvement in bulbar function; however, pooled data from the three studies

showed a decreased rate of decline in bulbar symptoms for patients who took the active drug compared to the placebo. All of these studies used the Norris scale as the primary outcome measure of bulbar symptoms. The Norris scale is a subjective scale that assesses a patient's ability to perform 13 tasks associated with bulbar muscles, and grades each on a three-point scale. There is no evidence of correlation of this scale to swallowing safety or efficiency. To date there has been no instrumental assessment investigating swallowing outcomes in response to Riluzole and the evidence for improvement in swallowing as a result of Riluzole is, therefore, limited.

Edaravone is an intravenous drug that has been approved in the United States of America (USA). The exact mechanism for success of Edaravone is unknown, but it is believed that the effects are due to the drug's ability to clear free radicals from the system. This may alter the course of MND by preventing oxidative stress (Abe et al., 2017; Cruz, 2018). The efficacy of Edaravone is inconclusive in the literature. In a study of 206 patients with MND, Abe et al. (2014) found no significant differences in outcomes for patients taking Edaravone compared to a placebo over a 24-week treatment period. A subsequent phase III trial indicated a significantly reduced rate of decline in patients who received Edaravone compared to controls (Takei et al., 2017). Participant recruitment in this study was more specific to avoid the previously observed flooring effects. However, the primary outcome measure used in these studies was the ALSFRS-R, which is often patient reported, and therefore allows for placebo influence. More research, with appropriate outcome functional and physiological measures, is necessary to determine the effectiveness of this drug and appropriate patient selection.

Neudexta, another prescribed drug, reduced the rate of deterioration compared to a placebo control group, as measured by the ALSFRS-R (R. Smith et al., 2017). Additionally, 30 days of Neudexta significantly decreased pause frequency and duration during speech, a measure that differentiates individuals with MND from healthy controls (J. R. Green et al., 2018; J. R. Green, Beukelman, & Ball, 2004). The impacts of Neudexta on other functional measures of speech and swallowing have been assessed but changes were not significant (J. R. Green et al., 2018; R. Smith et al., 2017). Neudexta is an antitussive agent (C. P. Taylor, Traynelis, Siffert, Pope, & Matsumoto, 2016); it is therefore possible that the patient reported improvements in the ALSFRS-R were a result of reduced sensitivity to airway invasion. Further research, including instrumental assessment of swallowing, is necessary to investigate

the effects of Neudexta on swallowing symptoms, particularly in terms to sensitivity to airway invasion.

Drug treatments are also used for symptom management. An example of this is the use of hyoscine patches and botulinum toxin to the salivary glands for management of sialorrhoea. Although these treatments may be effective for a period of time, as the disease progresses, they are often no longer adequate to facilitate elimination of the increasing symptom demand (Jenkins, Hollinger, & McDermott, 2014).

Because of the lack of effective prescribed medications, patients commonly explore alternative medications. These can be both unsafe and expensive but entice patients with the hopes of finding a cure, improving their condition or slowing the rate of symptom progression (Wasner, Klier, & Borasio, 2001). The ALSUntangled group is working towards providing clarity regarding the effects of alternative medication. This group summarises the risk and level of evidence for taking a given alternative treatment and publishes this in an open access journal and on their website (ALSUntangled, 2018). The website currently does not recommend any alternative medications for the treatment of MND.

4.2 Non-Invasive Ventilation

Non-invasive ventilation (NIV) is used to improve survival and quality of life in patients with respiratory insufficiency. NIV has been shown to improve symptoms associated with hypercapnia, including improved oxygen saturation and better sleep (Bourke et al., 2006; Vrijsen et al., 2015). Importantly, this has been demonstrated to improve quality of life as NIV results in a reduction of daytime fatigue and depression (Bourke et al., 2006). There is only one randomised controlled trial investigating the effects of NIV (Bourke et al., 2006). In this study, the use of NIV increased survival by seven months in patients without severe bulbar dysfunction; however, no significant improvements were found for patients with severe bulbar symptoms (Bourke et al., 2006). Following this trial, it was deemed to be unethical to withhold NIV to conduct further randomised control trials. More recent retrospective studies have demonstrated that the use of NIV increases survival by 11 to 15.5 months (Berlowitz et al., 2016; Hirose et al., 2018; Sancho et al., 2018). However, as these studies were not randomised controlled trials, these patients may have been more willing to undergo additional life sustaining procedures (e.g. PEG, drug treatments) than those who were in the no NIV cohort.

The literature regarding the use of NIV in patients with bulbar symptoms due to MND is less definitive. For patients with bulbar symptoms, labial weakness reduces the effectiveness of a nasal mask as air can escape through the mouth. Bourke et al. (2006) did not demonstrate a difference in survival in patients with severe bulbar dysfunction with and without NIV. However, the primary aim of this study was not to investigate patients with bulbar impairment and the sample size of patients with severe bulbar impairment was limited to 21 patients. Additionally, this research was performed in 2006, and technology and assessment procedures have since progressed. More recent research has demonstrated increased survival time as a result of NIV in patients with bulbar symptoms to be between 10 and 19 months. (Berlowitz et al., 2016; Dorst & Ludolph, 2019; Sancho et al., 2018). These studies were retrospective, not randomised controlled trials and as discussed previously, this may have led to bias. However, the significant effect of NIV on survival remained following adjustment for age, gender, Riluzole and PEG use (Berlowitz et al., 2016). This indicates that NIV likely increases survival in patients with bulbar symptoms and the potential increase in quality of life and life expectancy outweigh those of any drug assessed to date.

4.3 Palliative care

Due to the poor prognosis associated with MND, it is suggested that palliative care teams are involved from the time of diagnosis (Bede et al., 2011). The World Health Organisation defines palliative care as "…an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" (World Health Organization, 2018, para. 1). Palliative care does not aim to increase length of life but can help to manage symptoms such as pain, increase quality of life and reduce caregiver burden (Blackhall, 2012; Hogden, Aoun, & Silbert, 2018; Oliver et al., 2016).

5. Dysphagia assessment

Due to the range of symptoms experienced by patients with MND, multidisciplinary management is crucial (R. G. Miller et al., 2009). Attendance at a specialist clinic with multidisciplinary input results in fewer hospital admissions and an increased length of survival for these patients, due to more frequent monitoring of symptom progression and a

higher rate of intervention implementation (A Chio, Bottacchi, Buffa, Mutani, & Mora, 2006).

5.1 Screening for cognitive impairment in MND

It is important to understand a patient's cognitive function, as it may influence their ability to follow instructions and participate in treatment. There are many screening tools for cognitive impairment available; however, there is no consensus regarding which is the most appropriate for individuals with MND (R. G. Miller et al., 2009). The Mini-Mental State Examination (MMSE) is a commonly utilised screening tool for cognitive changes. However, the sensitivity of the MMSE is not sufficient to detect mild cognitive impairment (MCI) in MND as it does not assess executive dysfunction (R. G. Miller et al., 2009; Strong et al., 2009). The Montreal Cognitive Assessment (MoCA) is a screening tool that is more sensitive to detecting MCI (Folstein, Folstein, & McHugh, 1975; Nasreddine et al., 2005; Trzepacz et al., 2015). The MoCA screens for short-term memory recall, delayed recall, working memory, attention, concentration, visuospatial abilities, executive function, language and orientation to time and place, many of which can be affected by MND. The MoCA is a valid test with high test-retest reliability and internal consistency (Nasreddine et al., 2005). Assessment of cognition can be difficult in patients with MND due to concomitant motor speech and limb dysfunction. This means that timed assessments and tasks involving speech or writing may need to be avoided or altered to accommodate the needs of an individual.

5.2 Clinical assessment of swallowing

Although limited in its scope, a clinical swallowing assessment (CSA) can provide important information about functional swallowing. CSAs often include gathering information about a patient's history with or without the use of validated survey tools, assessment of cranial nerves and observation of oral intake. Some aspects of a CSA are outlined below. Advantages of the CSA are that it can be performed anywhere, it is inexpensive and it is easily repeatable. CSAs are often used to determine if further instrumental evaluations are necessary (Garand, McCullough, Crary, Arvedson, & Dodrill, 2020). In a survey of MND clinics in the USA, 55% reported completing a CSA as part of the routine assessment of patients with MND (Plowman, Tabor, Wymer, & Pattee, 2017).

5.2.1 Swallowing history

A thorough history of the presence and presentation of dysphagia is an integral part of the CSA. History of dysphagia is often gathered through a verbal interview. Targeted questions such as asking what a patient eats and drinks most days and if there are any foods that they avoid may give more insight into the presence of dysphagia than general questions, such as if a patient has difficulty swallowing (Garand et al., 2020). Validated questionnaires are a beneficial addition to a verbal interview to gather more information about the presence and effects of dysphagia.

The ALSFRS-R is a scale that is commonly used in the literature to determine a patient's level of function during various activities of daily living. It is a valid and reliable assessment consisting of 12 sets of statements, for which patients rate their ability to perform activities of daily living on a five-point scale (Cedarbaum et al., 1999). Bulbar symptoms are addressed in terms of speech, salivation and swallowing with the score of zero for "loss of useful speech", "marked drooling; requires tissue of handkerchief" and "NPO (exclusively parenteral or enteral feedings)" respectively, and a score of four for "normal" (Cedarbaum et al., 1999). Overall change in ALSFRS-R score over time is a sensitive predictor of survival, and it is therefore, widely used both clinically and in research trials (Kollewe et al., 2008). There is an inverse relationship between ALSFRS-R scores and dysphagia severity, indicating that gross changes in function are represented by changes on the scale (Ruoppolo et al., 2013). However, the bulbar subscale on the ALSFRS-R does not have sensitivity or diagnostic accuracy to detect changes in bulbar function, including the presence of dysphagia that is evident on instrumental assessment (Allison et al., 2017; Chapin et al., 2020; J. R. Green et al., 2013).

The Eating Assessment Tool (EAT-10) was created as a short screening tool for dysphagia that incorporates both physiological and psychosocial domains of swallowing (Belafsky et al., 2008). It is a ten item self-report questionnaire, in which patients rate their symptoms on a four-point scale, providing a total score out of 40. The EAT-10 was reported to have excellent internal consistency, test-retest reproducibility and criterion based validity (Belafsky et al., 2008). It is quick and easy to administer, and as such, has been translated into several languages including Spanish, Arabic and Swedish (Burgos et al., 2012; Farahat & Mesallam, 2015; Möller, Safa, & Östberg, 2016). A positive linear correlation between aspiration events and the EAT-10 has been demonstrated (Cheney, Siddiqui, Litts, Kuhn, &

Belafsky, 2015), and a score of three or higher has been found to be representative of the presence of dysphagia (Belafsky et al., 2008). In patients with MND, a score of three or higher has a sensitivity of 88% and specificity of 57% for predicting airway invasion with higher scores recorded for patients who aspirate (Plowman, Tabor, et al., 2016). Scores from the EAT-10 have also been shown to correlate with lingual speed in patients with MND (B. J. Perry et al., 2020). Recently, the construct validity of the EAT-10 was investigated by two similar studies using Rasch models (Cordier et al., 2017; Wilmskoetter et al., 2019). Both studies highlighted similar limitations of the survey in clinical and research practice. Two items of the EAT-10 ("I cough when I eat" and "My swallowing problem has caused me to lose weight") have been shown to misfit the model (Cordier et al., 2017; Wilmskoetter et al., 2019). Further, differential item functioning analyses highlighted four items with differential item functioning between patients who aspirate and those who do not. If there are inherent differences between groups on a scale, it indicates that the scale cannot be used to directly compare between patients in these groups, or within a patient if that patient moves between groups due to improvement or decline in swallowing. Further, the EAT-10 performs poorly at separating individuals into groups based on severity of dysphagia (Cordier et al., 2017; Wilmskoetter et al., 2019). It was found to be able to separate patients into 3 strata (e.g. no dysphagia, moderate and severe) in one study (Wilmskoetter et al., 2019) and less than two in the other study (Cordier et al., 2017). It is therefore unlikely to detect small changes over time or as a result of treatment. These limitations suggest that the EAT-10 is not an appropriate outcome measure and that care should be taken when using it to compare between patients e.g. as a screening tool. However, clinical benefit of the EAT-10 may remain as the questions asked can provide beneficial information regarding a patient's perspective of their swallowing difficulties.

Oropharyngeal dysphagia has a negative impact on the quality of life of patients with MND (Paris et al., 2013). For a therapist to provide appropriate care, and to measure meaningful outcomes of an intervention, it is necessary to have a means of gauging the extent of this impact on patients. The Swal-QOL obtains information pertaining to a patient's perception of their swallowing, and related quality of life factors. The Swal-QOL consists of 44 questions with subsections including eating desire and food selection (McHorney et al., 2002). Patients respond to each statement on the Swal-QOL using a five-point scale relating to the frequency of a symptom, or the level to which they agree with a statement. The Swal-QOL can be scored out of 100 in various categories, with higher scores indicating a better quality of life.

In a systematic review of literature investigating the use of self-reported assessments of swallowing for patients with progressive neurological disorders, the Swal-QOL was judged to be the questionnaire with the best combination of reliability, convergent validity and clinical application (Keage, Delatycki, Corben, & Vogel, 2015). Importantly, scores from the Swal-QOL can discriminate between MND patients with and without dysphagia under videofluoroscopy (Paris et al., 2013; Tabor et al., 2016). Paris et al. (2013) investigated this by comparing Swal-QOL outcome for patients with as without dysphagia determined by the dysphagia outcome severity scale on VFSS. Thirty patients were recruited, 14 with normal swallowing and 14 with oropharyngeal dysphagia. Interestingly, there was no difference in BMI between the groups. Patients with dysphagia scored significantly worse in the symptom frequency categories of pharyngeal, oral and salivary symptoms. Additionally, patients with dysphagia reported increased burden, eating duration, food selection, eating desire, fear, oral communication, mental heals and social factors. Patients in this study were only split into two groups based on presence or absence of dysphagia, so this study does not provide information regarding whether the Swal-QOL is sensitive to changes over time. Tabor et al. (2016) further investigated this relationship by comparing Swal-QOL outcomes to the penetration aspiration scale and the ALSFRS-R. In a group of 81 patients, a significant difference was found in Swal-QOL scores between patients who were identified as safe swallowers (n = 45), penetrators (n = 21) and aspirators (n = 15). Scores in the Swal-QOL were negatively correlated with PAS scores, indicating that patients with unsafe swallowing scored worse on the Swal-QOL. There was also a significant correlation between Swal-QOL and ALSFRS-R scores, demonstrating that changes in swallowing quality of life are associated with global progression of the disease. However, these are both self-reported questionnaires and further research documenting disease progression with alternative measures of patient functioning may help to confirm the results.

Romero-Gangonells et al. (2020) used VFSS to compare the sensitivity and specificity of commonly utilised scales: the Functional Oral Intake Scale, EAT-10, swallowing category from the ALS Severity Scale and the symptom frequency section of the Swal-QOL questionnaire. All scales demonstrated a low sensitivity and fair specificity at detecting dysphagia. The authors were able to increase sensitivity and specificity with a modified version of the Swal-QOL, indicating the need for development of a questionnaire that is specific to symptoms associated with MND (Romero-Gangonells et al., 2020).

5.2.2 Cranial nerve evaluation

Evaluation of the five cranial nerves associated with oral and pharyngeal phases of swallowing (CN V, CN VII, CN IX, CN X and CN XII) provides information regarding potential symptoms and causes of dysphagia. In MND, reduced strength and range of motion may occur for muscles associated with each of these cranial nerves (Hillel & Miller, 1989). During a cranial nerve evaluation, changes to strength and range of motion are often detected through observation or palpation of various motor movements (Hillel & Miller, 1989). However, there is no standard regarding what is considered adequate strength or range of motion, making the assessment highly subjective (Clark, 2005).

Cough reflex testing (CRT) is an adjunct to the traditional cranial nerve exam, which provides information about laryngeal sensitivity. CRT assists with clinical decision making by identifying patients with impaired laryngeal sensation, and therefore, the potential to silently aspirate. Use of the cough reflex test allows more efficient referral for instrumental examination (Miles et al., 2013; S. E. Perry, Miles, Fink, & Huckabee, 2019). CRT has been investigated in 32 patients with MND who were compared to 34 healthy controls. Individuals in this study inhaled nebulised capsaicin of varying concentrations following an instruction to "cough if you need to" (Tabor-Gray, Vasilopoulos, Wheeler-Hegland, et al., 2020, p. 3). Participants then rated their urge to cough using a Modified Borg scale and those with MND underwent VFSS. Increased urge to cough ratings were found for increased concentrations of capsaicin in both patients and healthy controls. During VFSS, one patient reflexively coughed to aspiration and five patients demonstrated silent aspiration (PAS = 8). During capsaicin trials, the patients who silently aspirated had blunted urge to cough sensitivity slopes and evoked cough response slopes. Two of the patients who silently aspirated reported zero urge to cough and no motor response to any concentration of capsaicin. However, there was a lot of variability between the other patients who demonstrated silent aspiration on VFSS. In the patients with who did not silently aspirate (n = 21), urge to cough of at least one was reported for all capsaicin trials. Cough motor response to capsaicin was absent in two patients who did not demonstrate silent aspiration. However, it is important to consider that there may be patients who did not aspirate during the VFSS but have impaired laryngeal sensation. Interestingly, patients with MND who did not aspirate demonstrated greater sensitivity to higher concentrations of capsaicin than healthy controls. Despite higher urge to cough ratings, patients showed reduced motor responses, suggesting reduced physiologic reserve.

This study did not provide information about the sensitivity and specificity of using cough reflex testing as a screening tool in patients with MND but highlighted physiological differences between patients and healthy controls. More information about cough reflex testing in this population is required before including it as a routine screening tool.

5.2.3 Swallowing trials

If deemed appropriate following a detailed case history and cranial nerve evaluation, a patient will perform trials of various foods and drinks. During oral trials, the clinician observes a patient for signs of dysphagia, including cough and changes in vocal quality (Garand et al., 2020). The observation of swallowing at bedside generally has low inter- and intra-rater reliability (McCullough et al., 2000). The validity and reliability of oral trials in patients with MND have not been investigated. However, oral trials are unlikely to identify all patients with dysphagia as silent aspiration is common (Goeleven et al., 2006; Lo Re et al., 2007).

The Timed Water Swallow Test (TWST) was developed as a simple, functional test to improve the predictive value of a bedside assessment and allow monitoring of change in swallowing capability. To complete the TWST, patients are presented with 150 mL of water if they are under 75 years of age or 100 mL if they over 75. They are asked to drink the water "as quickly as is comfortably possible" (Hughes & Wiles, 1996, p. 111) while the therapist records the number of swallows and the time taken for the patient to consume the water. From these measures, the average volume per swallow (mL), time per swallow (s) and the volume swallowed per sec (ml/s) can be calculated and compared to normative data. Normative data are stratified by sex and age group. Importantly, the TWST is effective in identifying swallowing changes secondary to MND, as scores for this population are significantly different from healthy controls (Hughes & Wiles, 1996). The TWST has highlighted a reduction in bolus size for patients with MND compared to healthy controls. For patients with MND, bolus size was 4 mL for females and 7 mL for males compared to over 10.5 mL for all healthy females and over 20 mL for healthy males (Hughes & Wiles, 1996).

The Test of Masticating and Swallowing Solids (TOMASS) is an adjunct to the TWST, which provides additional information about pharyngeal and oral phases of swallowing solids (Huckabee et al., 2017). It has been shown to be a valid measure of masticatory and swallowing efficiency, with high inter-rater and test-retest reliability (Huckabee et al., 2017).

The assessment protocol for the TOMASS is similar to that of the TWST. To complete the TOMASS, patients are presented with a cracker and given the instruction to eat it "as quickly as is comfortably possible and when you have finished, say your name out loud" (Huckabee et al., 2017, p. 147). As the patient eats a cracker the number of bites, masticatory cycles, swallows and the time taken to consume the cracker are recorded (Huckabee et al., 2017). When under the influence of topical oral anaesthesia, the number of chews and amount of time taken to complete the TOMASS is increased compared to baseline (Lamvik-Gozdzikowska, Guiu Hernandez, Apperley, McIntosh, & Huckabee, 2019). These results demonstrate that the oral phase contributes significantly to TOMASS outcomes and that the TOMASS is sensitive to detecting changes in oral sensation.

An important consideration when performing this assessment between locations is that there are implicit differences between crackers that are readily available around the world, and these differences have an effect on scores of the TOMASS (Huckabee et al., 2017). Normative data have been collected for the TOMASS using different types of crackers, which are available in various centres around the world including, but not limited to NZ/ Australia, the USA and the United Kingdom/ Ireland (Huckabee et al., 2017). Normative data for the TOMASS have been calculated for raw outcome measures and derived measures of masticatory cycles per bite, swallows per bite, time per bite, time per masticatory cycle and time per swallow. Due to the observed differences between cracker type and significant differences in performance as a result of age and sex, normative data are stratified by cracker type, age and sex (Huckabee et al., 2017).

5.3 Instrumental assessment of swallowing

CSAs provide limited information about safety and efficiency of swallowing or pathophysiology associated with dysphagia. Information attained through instrumental assessment is often more objective than clinical swallowing exams. Videofluoroscopic swallowing studies (VFSS) and flexible endoscopic evaluation of swallowing (FEES) are the most widely utilised instrumental swallowing assessments (Langmore, 2003). Pharyngeal manometry, ultrasound and surface electromyography are adjunct swallowing assessments that are emerging within the swallowing literature.

5.3.1 Flexible Endoscopic Evaluation of Swallowing

Flexible endoscopic evaluation of swallowing (FEES) allows visualisation of the hypopharynx, larynx and proximal trachea by passing a flexible endoscope trans-nasally (Hiss & Postma, 2003). Benefits of FEES are that it is portable, it does not involve harmful radiation and it allows direct visualisation and evaluation of extent of pharyngeal and laryngeal movements when performing non-swallowing tasks. FEES may be completed at a patient's bedside and can be repeated without additional risk. However, due to light reflection during epiglottic deflection there is a period of whiteout during the pharyngeal stage of swallowing. FEES, therefore, provides less information than VFSS regarding the extent of structural movement during swallowing and the pathophysiology of dysphagia.

There is discrepancy in the literature regarding the efficacy of FEES in patients with MND. Leder et al. (2004) reported that FEES was highly beneficial for patients with MND as it provided sufficient information to diagnose pharyngeal dysphagia and provide swallowing biofeedback, whilst being portable and safe enough to repeat over the course of disease progression. However, when compared to patient report and VFSS findings, FEES was not found to be sensitive in detecting dysphagia in patients with MND (Briani et al., 1998). Further, FEES is not always well tolerated in patients with MND, likely due to an increased gag reflex as a result of hyperreflexia associated with UMN dysfunction (Aviv et al., 2002; Cohen et al., 2003; Domer et al., 2013; Leder et al., 2004).

5.3.2 Videofluoroscopic swallowing studies

Videofluoroscopic swallowing studies (VFSSs) use x-ray imaging to allow visualisation of bolus flow, airway invasion and the extent and efficiency of structural displacement during the oral, pharyngeal and oesophageal phases of swallowing (Daniels & Huckabee, 2014). Both qualitative and norm referenced quantitative information can be acquired through VFSS, making it beneficial in the clinical and research settings. Despite the many benefits of VFSSs, Plowman et al. (2017) found that only 27% of sites, which participated in a survey of current clinical practice, routinely referred patients with MND for a VFSS. Clinicians reported various reasons for this, including that dysphagia is expected in this population and that the reaction to the presence of dysphagia would instigate referral for PEG, so knowledge of the specific pathology is not necessary (Plowman et al., 2017).

One disadvantage of VFSS is that radiation is necessary to produce videofluoroscopic images. Excessive doses of radiation can have an ionising effect on cells, which can result in skin burns and radiation sickness when exposed to large amounts over a short period of time and cancer if exposed to small amounts for an extended period. However, during a usual 4.82 minute clinical VFSS, a patient is only exposed to 1.23mSv of radiation (Kin, Choi & Kim, 2013), this is less than half of the radiation exposure (2.94mSv) that would be expected on a long haul flight (Enyinna et al., 2016) and approximately equal to the amount of natural background radiation a person would encounter in six months (Hendry et al., 2009). In a well-structured VFSS, the radiation exposure is low but assessments are time constrained and cannot be repeated on a regular basis. Although assessments should be time constrained, it is important to note that dose area product (DAP), the amount of radiation that is delivered to a patient, is not correlated with radiation exposure time (Bonilha et al., 2019). Therefore, timing of a study should not be the threshold for limiting radiation exposure during an exam. One major contributing factor to DAP was whether images were obtained in the anterior posterior (AP) or lateral projection due to the need for more radiation to penetrate the body in an AP view (Bonilha et al., 2019).

Radiation may be presented in either a continuous or a pulsed manner. In the continuous setting, the radiation is produced continuously over the period of time. The pulsed setting produces multiple short bursts of radiation, from which images are acquired. Pulsed radiation has multiple benefits; it reduces radiation exposure as there are greater periods in which the radiation is not on and it allows for less blurring of images as a result of motion artefact (Schueler, 2000). The frame rate is the number of individual images that are saved per second of fluoroscopy time. A higher frame rate results in more accurate interpretation of the study and a significant difference in recommendations has been observed for clinicians who reviewed a study at 15 and 30 frames per second (Bonilha et al., 2013). Bonilha et al. (2013) suggest 30 frames per second and 30 pulses per second when performing a VFSS, as this allows the examiner to visualise important transient effects of disordered swallowing.

VFSS typically has high intra-rater and low inter-rater reliability and various methods of analysis have been developed to increase consistency between raters (McCullough et al., 2001). Methods of analysis of VFSS include the Penetration Aspiration Scale (PAS) (Rosenbek, Robbins, Roecker, Coyle, & Wood, 1996), Dynamic Imaging Grade of

Swallowing Toxicity (DIGEST) (Hutcheson, Barrow, et al., 2017) and Dynamic Swallow Study (DSS) objective measurements (Leonard & Kendall, 2018).

The PAS is an eight point scale that quantifies the depth of airway invasion and an individual's response (Rosenbek et al., 1996). It was developed as a means of quantifying airway invasion to demonstrate changes in single patient. The PAS is commonly used in the dysphagia literature to detect change over time or in response to treatment. However, there are limitations to the use of this scale. Swallowing is often variable from one swallow to another and between boluses. It is therefore necessary to complete multiple swallows to determine a pattern. This creates difficulty in reporting PAS scores, as averaging over trials may result in decimal points, which are not included in the scale. As this is a descriptive scale, reporting a decimal point would not provide a useful description of a patient's swallowing safety. It is common for the worst score to be considered; however, this can skew the data to make the population appear worse than they are. A common mistake made by researchers is to treat the PAS as an ordinal or interval scale (Steele & Grace-Martin, 2017). However, for statistical purposes, data from the PAS should be considered categorical as it cannot be assumed that a higher score is a worse outcome than a lower score. For example, a score of three (material enters the airway, remains above the level of the true vocal folds and is not ejected from the airway) is often considered more severe than a score of four (material enters the airway contacts the true vocal folds and is ejected from the airway) (McCullough, Rosenbek, Robbins, Coyle, & Wood, 1998). The options for statistical analysis of a categorical scale are limited compared to that of ordinal or interval scales. Additionally, scores of 4 and 6 are very uncommon, which may indicate that these scores are not clinically relevant scores as they do not often or that they are events that are more often misreported (Rosenbek et al., 1996; Steele & Grace-Martin, 2017).

The DIGEST consists of subscales for efficiency and safety of swallowing. These subscales are then combined to produce an overall swallowing score. Safety is determined by airway invasion, using the criteria from the PAS, which are further modified by the number of events and degree of airway invasion. It is therefore subject to many of the limitations discussed above. Efficiency is determined by the amount of residue and modified by the type of bolus that resulted in residue. The DIGEST must be considered ordinal or categorical data and should be analysed as such, limiting its use in research studies. DIGEST was designed to be used with patients with dysphagia as a result of head and neck cancer (Hutcheson, Barrow, et

al., 2017), and transference of the scale to other populations such as MND has not been assessed. One potential limitation of using the DIGEST in patients with MND that has not been investigated is that it a categorical scale and may not account for small changes that occur in response to functional decline or treatment. The DIGEST has been used to investigate treatment effects in patients with MND (Plowman et al., 2019). Due to the ordinal nature of the scale, for statistical analysis Plowman et al. (2019) dichotomised DIGEST efficiency, safety and total scores. Dichotomising a variable reduces the variability in the data, which may lead to bias (Altman & Royston, 2006).

Objective measurements of DSS include quantitative analysis of timing (Kendall, McKenzie, Leonard, Gonçalves, & Walker, 2000) and structural displacement (Leonard, Kendall, & McKenzie, 2004) during pharyngeal swallowing. Normative values have been obtained for 1 mL, 3 mL and 20 mL thin liquid boluses. These measures are continuous, allowing for observation of a smaller degree of change than in DIGEST score. Further, specific instruction on how to perform measurements is provided to help to reduce the subjectivity involved in analysis. Structural displacement measures compare peak excursion to a pseudo-rest position obtained through a 1 mL bolus hold. These measures include pharyngeal constriction ratio (PCR), hyoid excursion and extent of UES opening. Each of these measures had an inter-rater reliability of greater than 90% when analysing VFSS's of healthy participants (Leonard et al., 2004). Timing measures include bolus transit time, timing of supraglottic closure and duration of UES opening and airway closure. All reported timing measures were found to have an inter-rater reliability of greater than 90% when assessing healthy individuals (Kendall et al., 2000). Temporal and kinematic measures from DSS have been used to measure change following swallowing treatment in patients with MND (Plowman, Watts, Tabor, et al., 2016); however, measurement reliability was not reported for this study. Significant improvements were reported for hyoid kinematics following treatment but no other significant differences were observed. Standard error for hyoid excursion was large indicating a high rate of variation between participants. Standard errors of the other measures were not reported. This large degree of variation on these measures for patients with MND may limit the ability to detect change in this heterogeneous population using the DSS.

5.3.3 Ultrasound

Ultrasound (US) is a non-invasive, safe, low-cost method of obtaining both quantitative and qualitative information about swallowing (Chi-Fishman, 2005). US converts electrical energy

into high frequency sound waves that pass through tissues of the body. Sound waves travel at a speed that is determined by the density and stiffness of the structure, known as the propagation speed (Aldrich, 2007). They are then reflected back to the transducer which allows visualisation of the boundaries between structures. Attenuation and/or alteration of a sound wave occurs as the wave passes through tissue. The predominant form of attenuation is absorption. This occurs as the US waves travel through soft tissue due to the friction of vibrating particles causing energy to be lost as heat. Rate of attenuation due to absorption is based on the frequency of the US wave. Higher frequency waves have a higher rate of attenuation and are less able to penetrate to deeper structures. However, higher frequencies have the benefit of increased spatial resolution. Clinical US is usually in the range of 2 MHz to 10 MHz (Aldrich, 2007).

An echo is the reflection of the sound waves, this is produced when there is a difference in the acoustic impedance of the tissues or structures and can be seen as a band. The larger the contrast in the density of the mediums, the darker the echo, as more of the sound wave is reflected back. At an intersection such as that between soft tissue and bone, a shadow is cast as none of the sound wave is able to travel through, so it is reflected (Aldrich, 2007). The method of image acquisition with US can affect the quality and reliability of images. Methodological considerations include the use of ample ultrasonic gel to create a barrier with no air gaps between the transducer and the patient's skin surface. This will reduce the reflection between air and soft tissue and substantially improve image quality (Aldrich, 2007).

US may be a beneficial tool for monitoring patients with MND as it is a non-invasive procedure that provides information regarding muscle mass and structural displacement, without the use of radiation. As US is low risk, it can be repeated to provide a quantitative measure of change in muscle cross sectional area over time. This may be beneficial in monitoring the atrophy of muscles and changes to structural displacement in patients with MND over time (Nakamori et al., 2015). For patients with potential MND, US has also been proposed as an adjunct to the diagnostic process as it can be used to visualise muscle fasciculations. When used in conjunction with needle EMG, US increases diagnostic accuracy when compared to needle EMG alone (Misawa et al., 2011; Nakamori et al., 2015; Tsuji et al., 2017). Denervation of a muscle can also be visualised via US, indicating LMN

dysfunction. This can be seen as an increase in echogenicity of the muscle (Simon, Noto, & Zaidman, 2016; Simon, Ralph, et al., 2015).

5.3.3.1 US of cross-sectional area of submental muscles

As previously discussed, the submental muscles are a vital muscle group for the opening of the UES and airway protection (Matsuo & Palmer, 2008). As they are close to the surface, the anterior belly of digastric muscles and the geniohyoid muscles can be safely viewed and measured with US (fig. 5.1). Ultrasound images of the cross-sectional area (CSA) of the anterior belly of the digastric muscles provide measurements that are highly correlated with those obtained by Magnetic Resonance Imaging (MRI) (Macrae, Jones, Myall, Melzer, & Huckabee, 2013). US imaging also provides additional information to MRI, as the technique allows for visualisation of the deeper geniohyoid muscles (Macrae et al., 2013).

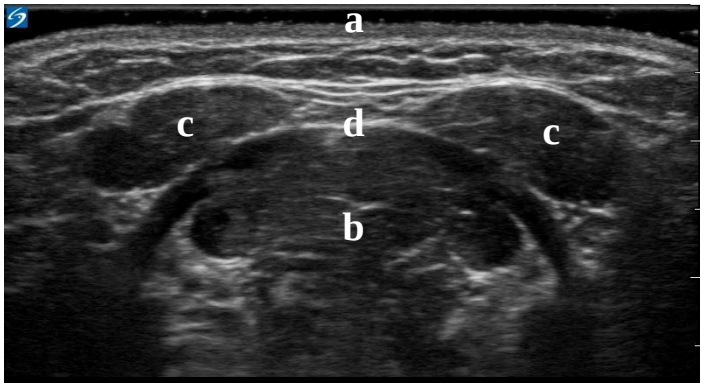

Figure 5.1: US of the submental muscles visualising: a) surface of the skin, b) geniohyoid muscles, c) anterior belly of digastric muscles, d) mylohyoid muscles.

5.3.3.2 US of dynamic swallowing

In addition to muscle CSA, US can provide quantitative information about dynamic features of swallowing such as hyoid excursion (figs. 5.2 and 5.3). As previously mentioned, due to the high difference in acoustic impedance, the boundary between soft tissue and bone results in an acoustic shadow, which allows both the hyoid bone and mandible to be easily visualised (Chi-Fishman, 2005). The acoustic shadow cast by the mandible is a good reference point for measuring displacement of the hyoid bone as alterations in patient or transducer position during swallowing will not influence the measurements (Macrae, Doeltgen, Jones, & Huckabee, 2012). With the use of US, significant differences can be seen in extent of hyoid displacement between patients and controls (Hsiao, Chang, Chen, Chang, & Wang, 2012).

There is good inter-rater and intra-rater reliability when analysing US videos of hyolaryngeal excursion in both healthy participants and patients with dysphagia (Hsiao et al., 2012; Macrae et al., 2012). Test re-test reliability is also high when images are collected by one individual (Shimizu et al., 2016). However, this high level of test-retest reliability could not be replicated with one of the emerging portable ultrasound devices (Winiker, 2019).

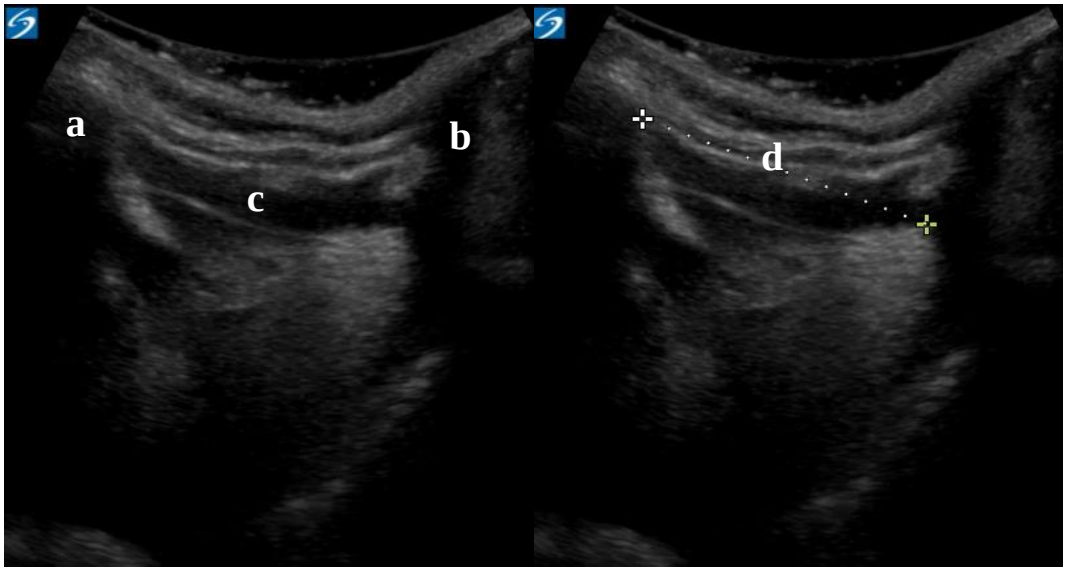

Figure 5.2. Measure of distance between the hyoid and mandible at rest: a) shadow of the hyoid b) shadow of the mandible c) geniohyoid muscle d) hyoid to mandible distance at rest

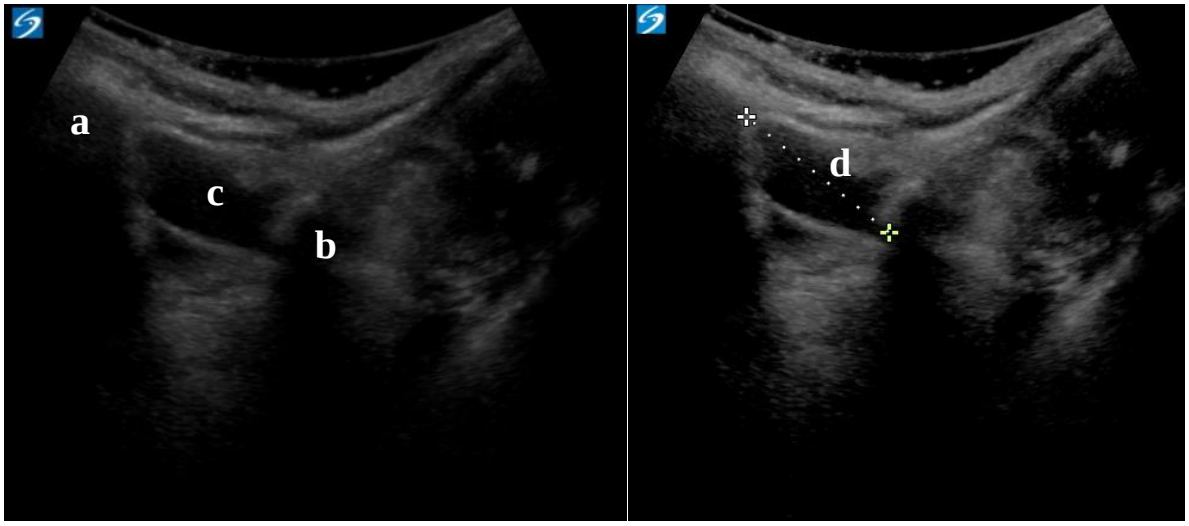

Figure 5.3. Measure of distance between the hyoid and mandible at rest: a) shadow of the hyoid b) shadow of the mandible c) geniohyoid muscle d) measure taken

Dynamic US has been investigated in patients with MND, using the thickness of the mylohyoid-geniohyoid muscle complex. The change in the thickness of the mylohyoid-geniohyoid muscle complex during swallowing, compared to the muscle at rest, was significantly lower in patients with bulbar onset MND compared to those with limb onset MND or healthy controls (Noto et al., 2017). This study did not compare dysphagic patients to non-dysphagic patients; this information would be beneficial in determining if this measure could indicate patients who would need to be followed up with further swallowing assessment. Interestingly, thickness ratio negatively correlated with measures of UMN but not LMN involvement, indicating that the reduction in muscle movement may be due to spasticity. However, it is important to note that although significant, the correlation between UMN involvement and mylohyoid-geniohyoid muscle complex thickness ratio was not strong ($r = -.53$; $p < 0.05$) (Noto et al., 2017).

5.3.4 Pharyngeal manometry

High resolution manometry (HRM) is frequently used for assessment of oesophageal motility and bolus transfer. More recently, this technique has been adapted to assess pressures in the pharynx during swallowing. HRM provides quantitative information about pharyngeal pressure generation, that can be extracted by an algorithm, removing any subjective bias (Mielens, Hoffman, Ciucci, Jiang, & McCulloch, 2011). However, highly variable pressure drifts have been reported that could not be corrected by standard correction strategies. These drifts in pressure can negatively impact both clinical and research use of HRM as pressure drifts can be close to one standard deviation of normal pressures (Lamvik, Guiu Hernandez, Jones, & Huckabee, 2016). Variability in methodology exists regarding both acquisition and analysis of HRM data. Significant variation exists in the literature between catheter size, HRM system used, use of anaesthesia and positioning of the patient. These methodological variations make comparisons between studies and the use of normative data difficult (Winiker, 2019).

HRM has documented reductions in pharyngeal pressure in patients with MND compared to healthy controls (Suh et al., 2019). Over the course of the disease, pharyngeal pressure continues to decrease and this can be monitored with manometry (Higo et al., 2004). To date, HRM has not been used as an outcome measure to investigate the effects of treatment in patients with MND. As HRM catheters are inserted transnasally, discomfort is common, and as with FEES, it may be difficult for patients with MND to tolerate due to a hyperreflexia.

The use of a topical nasal anaesthetic has been suggested to help reduce discomfort during catheter insertion. However, in healthy participants topical nasal anaesthetic has been found to have no benefits for comfort, and to result in reduced pharyngeal pressures when compared to a placebo (Guiu Hernandez, Gozdzikowska, Apperley, & Huckabee, 2018). The effects of topical nasal anaesthetic has not been investigated in patients with MND.

High resolution impedance manometry (HRIM) adds additional information about bolus flow to HRM (Daniels & Huckabee, 2014). A highly conductive, ionic compound such as saline (NaCl) is ingested during HRIM as it creates a closed circuit when it is positioned over proximal electrodes (Pandolfino & Kahrilas, 2009). The bolus position during swallowing can therefore be mapped, and residue is apparent with a sensitivity of 75% and specificity of 80% (Omari et al., 2011).

5.3.5 Surface electromyography

Electromyography (EMG) measures electrical signals produced by muscle contraction. The impulse from the motor neuron results in depolarisation and repolarisation of the muscle fibre, known as an action potential. Depolarisation of one neuron causes depolarization of adjacent neurons, which occurs in both directions towards the ends of the muscle fibre (Stepp, 2012). Depolarisation is associated with the transfer of Cl-, Na+ and K+ ions across the cell membrane and results in the creation of an electric field. The number of motor units recruited and their frequency of firing determines both the force that a muscle produces and the electrical signal created by the muscle contraction (Moritani, Stegeman, & Merletti, 2004). There is, therefore, a relationship between the surface EMG (sEMG) output and force produced by a muscle. However, sEMG is also influenced by a number of other factors including muscle fatigue, muscle temperature, skin-fold thickness, degree of synchronization of motor unit discharge, the muscle fibre potential, distance between electrodes and the position of the electrode on the muscle (Moritani et al., 2004; Vigreux, Cnockaert, & Pertuzon, 1980). The addition of these factors means that the relationship between the force produced and sEMG amplitude is not linear (Bilodeau, Schindler-Ivens, Williams, Chandran, & Sharma, 2003; Disselhorst-Klug, Schmitz-Rode, & Rau, 2008).

There are two methods of measuring EMG signals, intramuscular EMG and sEMG. Intramuscular EMG is invasive as it requires the insertion of a needle into the muscle. The use of intramuscular EMG increases the specificity of the signal, as readings can be taken

from specific motor units. Unlike intramuscular EMG, sEMG is a polyphasic signal, as it detects the action potentials generated from multiple motor units. The contribution of each motor unit to the signal is dependent on the distance between the motor unit and the electrode (Stepp, 2012). Layers of tissue between the electrodes and the muscles, including skin and subdermal fat, smooth and decrease the amplitude of the sEMG signal. Therefore, sEMG is most effective at measuring the activity of superficial muscles, such as submental muscles, as there is less signal dampening than for deeper muscles (Merletti, Botter, Troiano, Merlo, & Minetto, 2009; Stepp, 2012). During swallowing, sEMG allows for measurement of the activation of the entire submental muscle group, rather than a select number of motor units (Stepp, 2012). A significant benefit of sEMG is that it is non-invasive, and therefore, will not result in changes to behaviour as a result of discomfort as can occur with intramuscular EMG (Stepp, 2012).

During swallowing, the primary muscles that contribute to a reading of an sEMG electrode placed on the surface of the skin under the chin are the mylohyoid, geniohyoid and anterior belly of the digastric muscles (P. M. Palmer, Luschei, Jaffe, & McCulloch, 1999). However, more recent research has demonstrated that output from submental sEMG recordings can also be influenced by lingual activity during tasks such as effortful swallowing (Huckabee & Steele, 2006). As the submental muscles contribute to hyoid displacement during swallowing, there is a strong correlation between timing and extent of hyoid excursion and sEMG output (Crary, Carnaby, & Groher, 2006; Wheeler-Hegland, Rosenbek, & Sapienza, 2008).

In the dysphagia literature, sEMG has been used to provide quantitative information about the timing and extent of muscle activation during swallowing manoeuvres and functional swallowing tasks (Huckabee et al., 2005; Staudenmann, Roeleveld, Stegeman, & Van Dieën, 2010; Wheeler-Hegland et al., 2008). SEMG is sensitive enough to detect differences in bolus type and taste (Ding, Logemann, Larson, & Rademaker, 2003; Leow, Huckabee, Sharma, & Tooley, 2007). Increased amplitude of muscle activation has been recorded when swallowing thick consistencies and sour boluses, and longer duration of sEMG signal has been demonstrated with bitter boluses (Ding et al., 2003; Leow et al., 2007). One limitation of the current research investigating the use of sEMG for assessment of swallowing is that the majority of research has been performed with young healthy participants. Because of this, there is limited information about how submental sEMG data correlates with pharyngeal dysphagia.

6. Dysphagia management

The primary goals of dysphagia management are to maintain or improve safety and efficiency of oral intake. The outcomes from achieving these goals would be increased pulmonary safety, improved hydration and nutritional status and improved quality of life. Approaches to manage dysphagia can be subdivided into the categories of compensatory and treatment strategies.

Treatment for speech and swallowing disorders is not routinely provided to patients with MND (Beukelman, Fager, & Nordness, 2011). Management of worsening dysphagia in patients with MND has historically been restricted to the implementation of compensatory strategies and the use of PEG tubes for non-oral feeding (Kühnlein et al., 2008; Rosenbek & Troche, 2013). As previously discussed, patients with MND are seldom sent for instrumental swallowing assessments (Plowman et al., 2017). Without the use of instrumental assessment, there is the risk that recommended treatment or compensatory strategies will not be appropriate.

6.1 Compensatory strategies

Compensatory strategies aim to promote immediate change in bolus flow to increase safety or efficiency of swallowing. Two common approaches to compensation include diet modification (e.g. increasing thickness of fluids or pureeing solids) and postural changes (e.g. chin tuck or head turn). Compensatory strategies may increase the amount of time patients are able to eat orally. However, an important consideration with all compensatory strategies is that they do not alter the course of dysphagia progression and may in fact result in a reduction in range of motion, limiting true recovery of function, as has been observed in the limb literature (Takeuchi & Izumi, 2012). Therefore, in patients with a rapidly progressive disease, it is likely that a given compensatory strategy will be effective for only a short amount of time.

Diet modification is often recommended to patients with MND by speech-language therapists (SLTs) (Kühnlein et al., 2008; K. F. Luchesi, Kitamura, & Mourao, 2013). Pureed food can assist patients who have difficulty with mastication as the amount of oral preparation required for safe swallowing is reduced, thereby reducing fatigue across the meal. In this population, penetration and aspiration are more common with thin liquids than thicker liquids or solid

textures. Thickening liquids reduces the speed at which the liquids travel into and through the pharynx, which can lead to reduced depth of pre-swallow pooling and reduced aspiration. However, the amount of pharyngeal residue is often greater for thicker liquids (Dantas et al., 1990; Kuhlemeier, Palmer, & Rosenberg, 2001). When considering rates of aspiration, many studies consider only the first swallow and do not address the potential for airway invasion associated with pharyngeal residue (D'Ottaviano et al., 2013; Kuhlemeier et al., 2001; J. B. Palmer, Kuhlemeier, Tippett, & Lynch, 1993; Pizzorni et al., 2020). It is therefore likely that rates of airway invasion are under-reported for patients with significant post-swallow residue. Another consideration is that increased bolus viscosity leads to an increase in intrabolus pressure and requires greater lingual and pharyngeal muscle recruitment for bolus transfer (Dantas et al., 1990; J. L. Miller & Watkin, 1996). This increased effort could lead to greater fatigue over a meal and therefore put the patient at increased risk of aspiration, something that is not likely observed during short instrumental assessments.

Many patients with MND refuse thickened liquids (Onesti et al., 2017), perhaps due to the unpleasant taste, difficulty in social situations and discomfort associated with increased pharyngeal residue. In addition, serious adverse health outcomes may be linked to thickening liquids. In a study on rabbits, aspiration of thickened fluids was shown to be more harmful to the lungs than thin fluids, resulting in increased risk of pulmonary injury and death (Nativ-Zeltzer et al., 2017). Although information from animal studies cannot be directly compared to patients with dysphagia, this indicates the negative effects that thickener can have on body tissues. Thickened liquids have also been shown to lead to an increased incidence of dehydration, urinary tract infections and fever, and a reduction in patient satisfaction and quality of life (Davis, 2007; Robbins, Gensler, et al., 2008). There is not strong evidence in the literature that modifying food and liquid consistency is beneficial for patients with MND. Further, modification of diet should only be recommended following instrumental assessment because of the possible adverse effects and individual differences in response to various consistencies (Davis, 2007; Logemann et al., 2008).

Postural changes are often preferred by patients over diet modification (Logemann et al., 2008). Postural strategies change pharyngeal dimensions with the aim to redirect bolus flow. For example, the chin tuck narrows the laryngeal entrance, increases the duration of laryngeal vestibule closure and reduces the distance between the thyroid cartilage and the hyoid bone, resulting in decreased depth of airway invasion (Bülow et al., 1999; Macrae, Anderson, &

Humbert, 2014). For effective use of postural strategies, it is required that the patient has adequate cognition, attention and consistently adheres to the recommendations, as there is no effect once the posture is removed (Rasley et al., 1993). Postural modifications are often recommended to improve swallowing safety for patients with MND. The chin tuck, head turn and hyperextension of the neck have each been found to be effective at reducing airway invasion in specific patients (Solazzo et al., 2011). However, no strategy was effective for all patients, again highlighting again the need for instrumental assessment to determine appropriate management (Solazzo et al., 2011).

6.1.1 Non-oral feeding

Arguably, the most extreme compensatory approach to dysphagia is restriction of oral intake altogether. Non-oral feeding options such as nasogastric (NG) or percutaneous endoscopic gastrostomy (PEG) tubes allow nutrition and hydration to be delivered by bypassing the disordered swallowing system. There are risks associated with non-oral feeding options such as infection of the tube site, mechanical complications (e.g. blockage of the tube) and metabolic complications (e.g. refeeding syndrome) (Blumenstein, Shastri, & Stein, 2014). Importantly, although they may provide short term benefit for nutrition and hydration, as with other compensatory strategies, non-oral feeding options do not alter the pathophysiology of dysphagia.

A PEG tube may be utilised as a pre-emptive method to combat weight loss. The proportion of patients with MND who use PEG tubes varies between country and institution, with most respondents to a survey based in the USA reporting that 50-69% of patients receive PEG tubes (Plowman et al., 2017). There is disagreement in the literature regarding whether PEG use results in increased length of survival (Mazzini et al., 1995; Mitsumoto et al., 2003). For ethical reasons, randomised controlled trials investigating the benefits tube feeding for patients with MND do not exist. In a Cochrane review of the literature, Katzberg and Benatar (2011) concluded that the evidence for PEG feeding increasing survival in patients with MND was positive but weak. Further, a higher BMI has been reported for patients with MND who have a PEG compared to those who refuse PEG insertion (Mazzini et al., 1995). As randomised controlled trials cannot occur, it is important to consider that the use of PEG feeding in these studies was a decision made by the patient. PEG use is associated with increased use of other assistive devices, multidisciplinary care, medical assistance in the home and more frequent physician visits and hospital admissions (Mitsumoto et al., 2003).

These factors may contribute to the positive outcomes observed for patients who receive enteral nutrition.

In a disease with rapid progressive loss of function, quality of life is an important consideration. There is no strong evidence to support increased quality of life following PEG insertion. One small study showed no significant effect of PEG tubes on quality of life (Zamietra et al., 2012); however this was a retrospective study with no control group and only 11 patients in the PEG cohort. Further research investigating a larger cohort of 100 patients also demonstrated no significant change in quality of life for patients following insertion of PEG (Kurien et al., 2017). However, there was no control group so it cannot rule out that the use of PEG feeding stopped decline in quality of life with symptom progression. Changes in carer quality of life in response to PEG have also been assessed with no significant changes observed following PEG insertion (Kurien et al., 2017).

There are risks involved with the placement of PEG tubes that must be considered. Minor complications include tube displacement, tube obstruction, transient laryngeal spasm and localised infection. Serious risks include gastric haemorrhage, failure to place the PEG and death (R. G. Miller et al., 2009). Mortality in the 30 days following insertion of gastrostomy has been reported to be between 4% and 25% (Adriano Chiò et al., 2004; Czell, Bauer, Binek, Schoch, & Weber, 2013; Forbes, Colville, Swingler, & Group, 2004). It is recommended that PEG tube insertion is completed in the early stages of the disease as respiratory failure increases the risk associated with PEG placement (Simon, Huynh, Vucic, Talbot, & Kiernan, 2015). Therefore, if a patient's diagnosis is delayed or they do not decide immediately, some patients may not be appropriate for PEG tube insertion. Tube feeding is considered a predictor of aspiration pneumonia (Langmore et al., 1998) and the risk of aspiration pneumonia is therefore not a sound justification for PEG feeding (R. G. Miller et al., 2009). PEG is not an appropriate option for all patients and careful considerations of the potential risks and benefits must be made by patients and their carers before undergoing the procedure.

6.2 Cricopharyngeal myotomy

Both improvement and decline in swallowing function have been reported following cricophayrngeal myotomy for patients with MND. Wilson, Bruce-Lockhart, and Johnson (1990) performed VFSS on 27 patients with dysphagia secondary to MND, identifying seven

patients with cricopharyngeal dysfunction as the predominant factor affecting their swallowing. Six of the seven patients underwent cricopharyngeal myotomy and all but one of these patients demonstrated improvement in the diet level that they tolerated. The use of diet level is a subjective outcome measure and the study would have been strengthened by the inclusion of objective quantitative outcome measures pre- and post-surgery. Many studies investigating the benefits of myotomy did not use instrumental assessments and outcomes were patient perception, which has a large risk of bias due to its subjective nature (David, 1985; Lebo, Sangü, & Norris, 1976; Loizou, Small, & Dalton; Takasaki, Umeki, Enatsu, Kumagami, & Takahashi, 2010). In a single case design, it has been demonstrated that UES pressure can decrease at rest and during dry swallowing as a result of cricopharyngeal myotomy (Takasaki et al., 2010). However, the functional effects to swallowing were not investigated. Further research with the appropriate instrumental assessment is necessary to determine the benefits of cricopharyngeal myotomy in the small percentage of patients with MND who demonstrate hypertonicity of the cricopharyngeus muscle.

There are significant risks associated with cricopharyngeal myotomy in this population. The mortality rate following the procedure has been reported to be as high as 20% (David, 1985). With limited evidence for functional benefits, improvement in quality or quantity of life and high risks associated with the surgery, alternative options for managing dysphagia in MND are required.

6.3 Strength-based swallowing treatment

Treatment strategies aim to induce long term improvements in the safety and efficiency of swallowing, resulting in improved nutritional, respiratory and quality of life outcomes. Strengthening techniques are the most common and well researched form of dysphagia treatment (Clark, 2003). Strength training aims to increase the power, force and/or endurance of the targeted muscles (Clark, 2003; D. Jones & Rutherford, 1987); success of strength training, therefore, assumes muscle weakness as the underlying cause of dysphagia.

Common tasks for increasing the strength of the muscles of deglutition include effortful swallowing (Bülow, Olsson, & Ekberg, 2001), the Mendelsohn manoeuvre and the Masako manoeuvre (Fujiu, Logemann, & Pauloski, 1995). These tasks require the patient to swallow in a manner that recruits muscles to a greater extent than in habitual swallowing, thereby increasing muscle strength. Strength training exercises also include non-swallowing tasks that

recruit the target muscles. Examples of non-swallowing exercises include head-lift exercises (Shaker et al., 1997), chin tuck against resistance (Sze, Yoon, Escoffier, & Liow, 2016) and expiratory muscle strength training (EMST) (e.g. Pitts et al., 2009; Plowman et al., 2019; Plowman, Watts, Tabor et al., 2016; Troche et al., 2010; Wheeler, Chiara & Sapienza, 2007).

During swallowing, individuals are able to volitionally increase effort with associated increased muscle recruitment (Hiss & Huckabee, 2005). During effortful swallowing, individuals are simply instructed to swallow with effort. Changes to swallowing timing as a result of effortful swallowing have been observed, including longer duration of hyoid excursion, laryngeal vestibule closure and UES opening (Hind et al., 2001; Hiss & Huckabee, 2005). Effortful swallowing also results in pressure changes during swallowing, including increased oropharyngeal pressures and decreased pressure at the UES (Hind et al., 2001; Hiss & Huckabee, 2005). However, research has demonstrated no change in the amount of pharyngeal residue (Bülow et al., 2001) and no increase in amplitude or duration of intrabolus pressure (Bülow, Olsson, & Ekberg, 2002). Further, adverse effects of effortful swallowing have been reported. In a single case study of a patient with dysphagia following brainstem tumour resection, nasal redirection of the bolus developed following training of effortful swallowing (Garcia et al., 2004). Nasal redirection persisted with reduction seen only upon training of effortless swallowing. In healthy individuals, reduced anterior hyoid movement and reduced laryngeal excursion have also been documented as a result of effortful swallowing (Bülow et al., 1999). It is likely that this reduction in hyolaryngeal excursion is a result of the lack of specificity of the muscles recruited for the task. It is likely that during effortful swallowing the force produced by the large suprahyoid and pharyngeal constrictor muscles, which pull the hyoid posteriorly, is greater than that of the submental muscles, which facilitate anterior hyoid excursion (Daniels & Huckabee, 2014). Further, research in healthy older adults demonstrated increased pharyngeal residue and reduced pharyngeal shortening as a result of effortful swallowing (Molfenter et al., 2018). Therefore, although effortful swallowing may increase pressures in the distal pharynx and duration of swallowing movements, this does not appear to result in functional benefits and there are risks associated with this manoeuvre that must be considered.

The Mendelsohn manoeuvre was originally designed as a compensatory strategy to enhance bolus transfer through the UES. To complete the Mendelsohn manoeuvre an individual must hold their swallow at the peak of hyolaryngeal excursion. Prolonged hyolaryngeal excursion

was suggested as a method of increasing the duration of UES opening and facilitating bolus transfer through the UES. In small studies with healthy participants, when compared to normal swallowing, the Mendelsohn manoeuvre has been shown to increase the duration of anterior and superior hyolaryngeal excursion with subsequent delayed closure of the UES (Kahrilas et al., 1991), increased submental muscle contraction (Wheeler-Hegland et al., 2008) and increased pharyngeal peak contraction and contraction duration (Boden, Hallgren, & Witt Hedström, 2006). More recently, the Mendelsohn manoeuvre has been investigated as an exercise for patients with dysphagia. Following two weeks of treatment with sEMG biofeedback, significant improvement in superior hyoid excursion was observed; however, there were no significant changes to anterior hyoid excursion or UES opening (McCullough & Kim, 2013). The authors suggested a potential improvement in skill rather than strength and as a result, increased coordination in swallowing timing measures (McCullough & Kim, 2013).

The Mendelsohn manoeuvre is a very difficult task to explain and comprehend, and if not done correctly it may not produce the expected results. One study using VFSS during the Mendelsohn manoeuvre reported that 24% of participants were unable to complete the task correctly (Wheeler-Hegland et al., 2008). One method of increasing accuracy is the implementation of biofeedback. However, consideration of the type of biofeedback is essential. In a small group of patients with dysphagia, duration of submental muscle activation measured by sEMG had no correlation with duration of maximum hyoid elevation or duration of laryngeal vestibule closure, indicating limitations of the use of sEMG for this training (Azola et al., 2015). Videofluoroscopy has been demonstrated to be a more effective method of training prolonged laryngeal vestibule closure (Azola et al., 2017); however, given the limitations of repeated VFSS, it is unlikely to be a feasible training approach.

The Masako manoeuvre was developed based on an observation that following surgical resection of oral cancer, the degree of anterior bulge of the posterior pharyngeal wall increased (Fujiu et al., 1995). To mimic the loss of posterior base of tongue movement and facilitate bulging of the posterior pharyngeal wall, the Masako manoeuvre involves swallowing with the tongue held between the front teeth (Fujiu & Logemann, 1996). Importantly, this strategy resulted in increased residual when performed with a bolus, and is therefore, recommended for strengthening purposes with saliva swallows only. The Masako manoeuvre has been shown to increase hypopharyngeal pressure in patients with base of

tongue resections (Lazarus, Logemann, Song, Rademaker, & Kahrilas, 2002) but not in healthy volunteers (Doeltgen, Macrae, & Huckabee, 2011; Doeltgen, Witte, Gumbley, & Huckabee, 2009). In healthy individuals there were no significant changes to swallowing function or biomechanics following four weeks of training (Oh, Park, Cha, Woo, & Kim, 2012). It therefore remains unknown whether the Masako manoeuvre would benefit patients with dysphagia due to reduced base of tongue to posterior pharyngeal wall contact but normal anatomy.

One example of a strengthening task that does not involve swallowing is the head-lift exercise. The head-lift exercise was designed to increase floor of mouth muscles to facilitate anterior hyoid movement (Shaker et al., 1997). This is done through patients lying supine and lifting their head to look at their toes. In healthy elderly individuals, six weeks of the head lift exercise has been shown to increase laryngeal excursion and UES opening (Shaker et al., 1997). Following treatment with the head-lift exercise, patients with dysphagia have demonstrated significant improvements in UES opening and anterior laryngeal excursion with resultant return to oral feeding in all 27 participants (Shaker et al., 2002). Compliance to this task has been reported to be a barrier with up to 50% of patients of individuals dropping out in the first two weeks of training (Easterling, Grande, Kern, Sears, & Shaker, 2005). Reported reasons for drop out included neck muscle soreness and dizziness (Easterling et al., 2005). The participants included in this trial were healthy elderly individuals and may, therefore, have had little motivation for continuing the trial. In the patient trial, participants also reported minor neck muscle discomfort; however, this discomfort was not significant enough to result in discontinuation of treatment (Shaker et al., 2002).

Adaptations have been made to the head-lift exercise to reduce the risk of dizziness and muscle aches. The chin tuck against resistance (CTAR) is one example. To complete the CTAR an individual places a rubber ball under their chin and presses down against the ball into a chin tuck position (Yoon, Khoo, & Liow, 2014). Subjective ratings by healthy individuals indicate that the CTAR is perceived to be less strenuous than the head lift exercise (Sze et al., 2016). However, the CTAR has not yet been systematically evaluated in a patient population. Measurement of fatigue with sEMG analysis of the submental muscles has been used to determine the specific muscles using during the head lift exercise and CTAR (Sze et al., 2016). Levels of submental muscle use and subsequent fatigue were equal during the CTAR and head-lift in healthy older participants. However, the CTAR was more specific

to this target muscle group, as greater fatigue was recorded in the sternocleidomastoid muscles during the head-lift exercise. This indicates that the CTAR may be a more appropriate task for improving dysphagia in patients with submental muscle weakness. However, sEMG signals during the CTAR may have been distorted due to contact between the ball that provided resistance for the exercise and the submental sEMG electrodes, indicating the need for further research investigating the potential use of this less strenuous alternative to the chin tuck exercise.

Expiratory muscle strength training (EMST) was originally investigated in the respiratory literature to assist with cough production (Smeltzer, Levietes, & Cook, 1996). However, this approach may have cross system benefits for swallowing. In addition to recruiting the muscles of expiration, when the EMST device is set to 75% of an individual's maximum expiratory pressure, the submental and palatal muscles are activated with a longer duration and higher amplitude than during water swallowing (Hutcheson, Hammer, Rosen, Jones, & McCulloch, 2017; Wheeler-Hegland et al., 2008; Wheeler, Chiara, & Sapienza, 2007). The most commonly used device in the dysphagia literature is the EMST150. It is a device with a one-way spring-loaded valve that provides resistance to forced expiration. The device is adjustable and can be set to a resistance that is appropriate for a given patient, allowing for increased or decreased difficulty as the resistance is changed. Patients are instructed to blow into the device such that the valve opens. In addition to healthy individuals, EMST has been investigated in many patient populations, including patients with neurodegenerative disease. One large randomised controlled trial has investigated the use of EMST in patients with Parkinson's disease (Troche et al., 2010). Sixty participants with mild to moderate dysphagia were recruited and randomised into receiving either the sham or active treatment. Patients in the active EMST group demonstrated increased hyoid excursion and decreased penetration aspiration scores measured by VFSS. This study demonstrated the potential benefits of EMST for facilitating airway protection in patients with mild to moderate dysphagia due to neurodegenerative disease. The use of EMST in patients with MND is discussed in the chapter 6.3.1.

The theory behind non-swallowing strengthening exercises is that if a patient is not able to achieve adequate muscle contraction for safe and efficient swallowing due to weakness, isolated strengthening of targeted muscles may translate to the functional task. However, sport and exercise literature has demonstrated that increases in muscle strength following

training are greater in the task that was trained than in other tasks that recruit similar muscles in a different manner (Rasch & Morehouse, 1957). Further, sport and exercise literature suggests that generally increasing the strength of a muscle group is not likely to be beneficial in improving performance in a specific task (Burkhead, Sapienza, & Rosenbek, 2007), highlighting the importance of task specificity.

There has been little research investigating the required intensity for strength training to improve swallowing function. Information from sport and exercise science indicates that to achieve muscle hypertrophy and increase force generation, the task must include repetitive execution at a magnitude above the habitual level (Rasch & Morehouse, 1957; Zatsiorsky & Kraemer, 2006). It is recommended that a task is initially at an intensity of at least 60% of a one rep maximum, but 70-85% is preferable for inducing high rates of muscle hypertrophy (Burkhead et al., 2007; Porter, 2000; Wernbom, Augustsson, & Thomeé, 2007). Research has not indicated the most beneficial intensity for hypertrophy of bulbar muscles; however, progressive strength training regimes with loads above 60% have demonstrated beneficial effects for patients (e.g. Robbins et al., 2007; Troche et al., 2010).

Although, in the past, strength training was the only option for dysphagia treatment, evidence is emerging that it might not be appropriate for all patients. Potential adverse effects have been identified following the effortful swallowing technique, including nasal redirection (Garcia et al., 2004) and reduced hyoid excursion (Bülow et al., 1999). In sport and exercise literature, strength training has been shown to result in impaired performance due to fatigue (Ament & Verkerke, 2009; Grandou, Wallace, Impellizzeri, Allen, & Coutts, 2020). Further, effects from a period of strength training are not permanent; following the offset of strength training exercises, detraining effects are a well-recognised phenomenon in respiratory and bulbar muscles (Baker, Davenport, & Sapienza, 2005; Burkhead et al., 2007; Clark, O'Brien, Calleja, & Corrie, 2009; Oh, 2015; Troche, Rosenbek, Okun, & Sapienza, 2014).

6.3.1 Strength training for individuals with MND

Exercise is not a common treatment approach in patients with MND. This is due to the belief that exercise will result in overuse of muscles, leading to increased levels of fatigue, and consequently, more rapid decline in function (Bennett, 1958). There is basis behind this concern as Carreras et al. (2010) demonstrated, through a mouse model of MND, that mice who underwent high intensity treadmill exercise had an earlier onset of motor symptoms than

sedentary controls. However, the same study showed that moderate intensity exercise was beneficial when compared to no exercise. Improvements were observed in body weight, motor performance and motor neuron counts of mice in the moderate intensity group (Carreras et al., 2010). In this study, moderate intensity differed from high intensity exercise based on the duration (30 vs. 60 mins), sessions per week (3 vs. 5) and speed (10 vs 20 meters/min) of exercise. Therefore, it remains unknown if one or a combination of these factors contributed to the differences observed between the groups.

Studies that have investigated exercise in patients with MND range from single case studies (Bohannon, 1983; Dworkin & Hartman, 1979; Watts & Vanryckeghem, 2001) to randomised controlled trials (Cheah et al., 2009; Clawson et al., 2018; Dal Bello-Haas et al., 2007; Drory, Goltsman, Reznik, Mosek, & Korczyn, 2001; A. C. Pinto et al., 1999; Plowman et al., 2019). The exercises that have been investigated include limb resistance training (Bohannon, 1983; Clawson et al., 2018; Dal Bello-Haas et al., 2007; Drory et al., 2001) treadmill training (Braga, Pinto, Pinto, & de Carvalho, 2018; S. Pinto, Swash, & de Carvalho, 2012; Mohammed Sanjak, Bravver, Bockenek, Norton, & Brooks, 2010), inspiratory muscle strength training (Cheah et al., 2009; S. Pinto & de Carvalho, 2013; S. Pinto et al., 2012) oral motor exercises (Dworkin & Hartman, 1979), Lee Silverman Voice Treatment (Watts & Vanryckeghem, 2001) and expiratory muscle strength training (EMST) (Plowman et al., 2019; Plowman, Watts, Tabor, et al., 2016).

The primary goal of resistance exercise is to increase or maintain the force that is able to be produced by the trained muscle through muscle hypertrophy. One of the first studies to investigate resistance exercises in patients with MND was a case report by Bohannon (1983). This study investigated the use of an isometric strength training protocol using a latex band for resistance when performing elbow flexion and extension exercises over 75 days. This patient increased strength in the trained muscle groups; however, this did not transfer to functional improvements. Further research in larger cohorts has examined changes in functional measures. Drory and colleagues (2001) investigated the use of individualised programmes for increasing strength of the limbs and trunk in 14 patients with MND compared to 11 patients who performed only their usual daily activities. The exercise programme aimed to work individuals against a moderate load for 15 minutes, twice daily. Patients were assessed at three, six, nine and twelve months. Drop-out rates were high in both the treatment and control groups so only three- and six-month assessments could be

compared. Participants in the treatment group had less decline in the ALSFRS-R compared to those in the control group at three months but there was no significant difference at the six-month assessment. ALSFRS-R is a common method of measuring functional change in this population. However, it is a subjective assessment that provides scores on broad categories of function, and therefore, may not be appropriate as a primary outcome measure in research trials. This is the only study that has investigated the impacts of exercise on spasticity in patients with MND. Significant differences were observed between the treatment and control group on the Ashworth scale at the three month assessment (Drory et al., 2001). However, this was not significantly different at the six-month assessment. Although it is widely used for measuring spasticity, the Ashworth scale is subjective, and scores are not significantly associated with electromyographic parameters in patients with upper motor neuron syndromes (Fleuren et al., 2010). Therefore, changes in spasticity as a result of exercise have not been well investigated for patients with MND.

One major barrier to participation in treatment is travelling to the clinics. Therefore, home based resistance exercise was investigated in 27 patients who were assigned to either the treatment or the usual care control group (Dal Bello-Haas et al., 2007). Again, the primary outcome measure was the ALSFRS-R. As in previous research there was a high drop-out rate with eight participants in the treatment group and 10 in the usual care group finishing the trial. Of the participants that did not drop-out, overall treatment compliance was reported to be high. ALSFRS-R and quality of life scores were higher in the treatment group than the control at the three- and six-month assessments. Additionally, measures of maximum isometric contraction declined significantly less in the treatment group at the six-month assessment, indicating potential benefits of long term use of exercise to maintain function. Kitano et al. (2018) investigated the use of an unsupervised home-based treatment programme that included strength training and stretching of both the upper and lower limbs and functional training exercises such as standing from a chair. Of the 21 participants recruited, 15 completed six months of home-based exercises and outcomes were compared to a historical control group of 84 patients who had participated in six months of supervised treatment. No adverse effects were observed in the at home treatment group, indicating that this is a safe method of exercise provision. However, there was still a high rate of drop out. Interestingly, when compared to historical controls, patients in the at home treatment group had a significantly higher respiratory function subscore and total score on the ALSFRS-R following treatment. This is likely a result of different exercises performed between patients

in the treatment group and historical controls. Specific information is not provided regarding the exercises completed by either group. It is also important to consider changes in healthcare systems over time when comparing a group to a historical control group. The dates that data was collected from the historical group were not reported and neither were factors such as medications taken by participants.

High drop-out rates are a significant factor of all resistance exercise regimes completed in the MND population. Clawson et al. (2018) compared the tolerability and effects of range of motion, endurance and resistance exercises in home-based training programmes on 59 patients. The training programmes were individually designed by a physical therapist and lasted six months. At the six-month point, 19 participants remained in the range of motion group, 14 in the resistance exercise group and 11 in the endurance exercise group. Compliance to the task was lowest in the endurance exercise group and highest in the range of motion group. None of the exercises were deemed to be harmful and there were no significant differences between groups in any of the outcome measures assess including fatigue, ASLFRS-R or quality of life. However, a trend towards fewer falls was noted in the resistance and endurance exercise groups. This study demonstrates safety of a range of exercise types but reduced compliance in endurance tasks.

One study (n = 5) has demonstrated potential negative effects of resistance training with loss of strength and power following a 12-week training period (L. Jensen et al., 2017). Interestingly, despite this, an improvement was observed in a functional chair rise task. In this study, a range of strengthening exercises targeting the upper and lower body were completed on non-consecutive days, two to three times per week with supervision from a clinician. In the absence of a control group, it is difficult to determine whether the observed negative changes were a result of disease progression or the exercise regime.

A pilot study investigating the safety of treadmill exercise recruited nine participants (Mohammed Sanjak et al., 2010). Exercise consisted of five-minute training blocks with five-minute breaks, for thirty minutes total. This was performed three times per week for a total of eight weeks. Of the original nine participants, one third dropped-out prior to finishing the protocol. For the participants who completed the protocol, gait speed, distance and stride length increased significantly in a six-minute walking test at both four and eight months of training. This study concluded that repetitive rhythmic exercise is well tolerated and indicated the need for further research.

As intensity is a limitation for exercise in patients with MND, Braga et al. (2018) investigated the effects of aerobic treadmill exercise with cardiopulmonary exercise testing to determine the intensity. All participants (n = 48) participated in range of motion exercises, limb relaxation, trunk balance and gait training and those in the treatment group had two additional sessions of moderate intensity aerobic exercise per week, with cardiopulmonary testing. Participants were selected to participate in the training or control group based on proximity of living to the hospital. Decline in ALSFRS-R score was observed in both patient groups; however, greater decline was observed in the control group. Importantly, although not statistically significant, patients in the control group had a higher mean age, had a higher percentage of women and a higher percentage of bulbar onset disease type, all predictors for a faster rate of decline. To account for this difference, the authors used a multiple linear regression model that included disease onset type, age and gender and with this demonstrated that the intervention group was an independent predictor of decline in ALSFRS-R score. This demonstrates that monitoring muscle fatigue during aerobic exercise may be beneficial to prescribing appropriate intensity exercise.

Inspiratory muscle strength training has been investigated by a number of authors with inconclusive results (Cheah et al., 2009; S. Pinto & de Carvalho, 2013; S. Pinto et al., 2012). Cheah et al. (2009) investigated the effects of 12 weeks of training with resistance gradually increased from 15% to 60% of a participant's maximal sniff nasal inspiratory pressure. Participants in both the treatment (n = 9) and sham groups (n = 10) demonstrated an increase in inspiratory muscle strength following the 12 weeks. This increase in strength was greater in the treatment group, but between group differences were not statistically significant. None of the improvements in strength remained following the offset of training. S. Pinto et al. (2012) investigated the effects of twelve weeks of inspiratory pressure training set at 30-40% of a participant's maximal inspiratory pressure using a randomised delayed-start design trial. No significant differences were observed between the treatment and the placebo groups in this trial. S. Pinto and de Carvalho (2013) then investigated longer term use of inspiratory muscle training set at 30-40% of an individual's maximum inspiratory pressure. Eighteen participants from the previous trial continued training for at least eight months. Outcomes from this group were compared to historical patient data that were matched for gender, age at onset, bulbar vs spinal onset, diagnostic delay, ALSFRS and respiratory test outcomes. There was a significant increase in survival time of approximately 12 months in the treatment group

compared to controls. However, it is important to consider the limitations of a historical control group when compared to a group that are motivated to participate in treatment.

In the studies that investigated outcomes after a period of no treatment, no differences between control and treatment groups were found at follow-up assessments two to six months following treatment (Cheah et al., 2009; Drory et al., 2001). These findings are consistent with literature that suggests that increases in muscle strength are not maintained following the conclusion of strength training.

Research investigating treatment for dysarthria includes two case studies (Dworkin & Hartman, 1979; Watts & Vanryckeghem, 2001). In these studies, a reduction in function following treatment was reported. However, both of these studies were single case designs with no manner of controlling for disease progression. Watts and Vanryckeghem (2001) investigated the outcome of oral motor strengthening, voice and articulation treatment, including Lee Silverman Voice Treatment, on a patient with MND. The voice of this patient was reported to be hoarse, strained and pressed, with ventricular fold phonation. There was not a strong rationale for the choice of treatment approach. Following completion of the protocol, the patient demonstrated decreased vocal quality and increased frequency of voice breaks. This study did not have controls and, as MND is degenerative, it is difficult to separate whether the negative results were in response to the treatment or natural disease progression. Dworkin and Hartman (1979) investigated the effects of lingual resistance exercises and a palatal lift on a patient with moderately impaired speech and swallowing. The treatment protocol was not well defined, with no indication of timing, number of sessions or specific exercises completed. They found continued decline in articulation and phonation, which was attributed to the progressive nature of the disease. The authors concluded that because of the rapid deterioration associated with MND, they were unable to confirm or deny the effects of the treatment protocol.

Strength training has also been assessed to treat dysphagia with the use of EMST (Plowman et al., 2019; Plowman, Watts, Tabor, et al., 2016). Plowman and colleagues (2016) initially investigated the feasibility of an EMST protocol in 15 patients. To ensure the exercise was at a mild to moderate intensity, the device was set at 50% of an individual's maximum ability. Other aspects of training intensity such as number of repetitions per session and number of sessions per week remained consistent with previous EMST literature, with five sets of five repetitions per day, five days per week (Hegland, Davenport, Brandimore, Singletary, &

Troche, 2016; Park, Oh, & Chang, 2017; Troche et al., 2010). EMST was well tolerated and resulted in improved respiratory and swallowing outcomes as measured by maximum expiratory pressure and anterior hyoid displacement.

In a subsequent randomised controlled trial, 48 patients with MND received eight weeks of treatment with either an EMST150 or a sham device (Plowman et al., 2019). Other training parameters remained the same as the pilot study, with one visit from a clinician per week and the remainder of the sessions performed independently. Patients in both the EMST and sham groups demonstrated increased maximum expiratory pressure (MEP) at the end of the 8-week treatment period, likely associated with a learning effect. However, patients in the active treatment group had a significantly greater increase in MEP than those in the sham group, indicating that there was a positive effect of the treatment on respiratory function. Swallowing safety was dichotomised into "safe" and "unsafe" with a cut-off score on the PAS of ≥ 3. Swallowing efficiency was dichotomised into "efficient" and "inefficient" with a cut-off score ≥ 1 on the efficiency subscale of the DIGEST indicating inefficient. Patients were also classed as "dysphagic" and "non-dysphagic" depending on whether total DIGEST total score was ≥ 1. This method of analysis may have led to some bias in the results as the variability in the data was reduced (Altman & Royston, 2006; Steele & Grace-Martin, 2017). Following treatment, decline in swallowing function was observed in both groups. However, there was a statistically significant difference reported between groups for swallowing efficiency. Significantly greater decline was reported in the sham group compared to the active treatment group. However, this change may not be clinically significant as pre-treatment both groups had two inefficient swallowers (pharyngeal residue $> 10\%$ of bolus) and following the eight-week protocol, the treatment group had three inefficient swallowers and the sham group had five inefficient swallowers, from 23 individuals in each group. Further, while only one patient demonstrated improvement in safety in the active treatment group, four patients demonstrated improvement in safety in the sham group; however, this was not statistically significant. Data from all of the 23 participants in each group who were reported to complete the protocol, were not included in all analyses. In the sham group, analysis of swallowing efficiency was performed on only 19 participants pre-treatment and 21 participants post-treatment. The authors do not describe the reasons for participants not to be included in the analyses. Considering that the difference in the number of patients moving from efficient to inefficient was only two patients, it may have made a significant difference to the outcome if the results from all patients were reported. Despite improvements in hyoid

displacement during the pilot study, changes in hyoid excursion were not reported for the randomised control study.

Although the submental muscles are used to complete EMST, swallowing is not involved in the task. As previously discussed, sport and exercise literature suggests that generally increasing the strength of a muscle group is not likely to improve performance in a task that is not trained (Burkhead et al., 2007). This could have contributed to change in outcomes for maximum expiratory pressure, the task that was trained, being more compelling than swallowing outcomes. These studies provide some evidence that EMST may be beneficial at prolonging swallowing function and improving respiratory outcomes in patients with MND, but more research with a larger sample size and continuous outcome measures would be beneficial.

Lingual strengthening has also been investigated in a small study of two participants with MND (Robison, 2015). This study demonstrated an increase in lingual endurance but not in lingual strength following the eight-week treatment program and there was no transfer to functional speech or swallowing tasks. Due to concern for over exertion, the strengthening load was at 50% of the initial one rep maximum, whereas the duration of the endurance task increased weekly. This study suggests that five repetitions of a 50% maximum task are not sufficient for increasing lingual muscle strength in patients with MND, investigations in a larger cohort would be necessary to confirm this.

Although evidence exists that strength training may be beneficial for patients with MND in improving respiratory and limb muscle function, there is currently no compelling evidence that it results in beneficial changes to swallowing. It is possible that due to the heterogeneity of dysphagia within this population there will be no one answer that facilitates improvement in all patients. Further research is needed to investigate outcomes of various treatment options for swallowing in this population.

6.4 Skill-based training for swallowing

Swallowing is a task performed at a submaximal strength. Therefore, although a patient may demonstrate muscle functioning at a level that is below what is considered normal, this may not cause dysphagia. Skill training is an emerging approach in the dysphagia literature that targets cortical modulation of swallowing. Although it is a recent addition to the dysphagia literature, skill training is not a new concept; it has been investigated for decades in the limb

literature. Skill learning is the process of increasing the spatial and temporal precision of a movement through practice (Willingham, 1998). Skill acquisition is the systematic improvement in performance accuracy without an associated decrease in speed (Kitago & Krakauer, 2013). There is some overlap between strength and skill training as there are aspects of both strength and skill involved in most tasks. Skilled learning and neural adaptation occur within many strength training paradigms, especially during the early stages as individuals learn the motor sequence and to maximally activate the antagonist muscles with minimal activation of agonist muscles (Folland & Williams, 2007). Conversely, repetition of a skilled task may increase the strength and endurance of muscles. However, the aim of the systemic adaptation differs between strength and skill training. While strength training aims to increase the size and strength of the peripheral muscle, skill training involves increasing precision of performance, and shifts focus to adaptation of central control of task completion (J. L. Jensen, Marstrand, & Nielsen, 2005).

Although an individual may have the capacity to perform an activity, 'skill' implies a quality of performance that must be acquired (Adams, 1987). Improvement at a skilled task is attained by increasing the accuracy of the task while increasing or maintaining the speed of performance; this is achieved through task repetition and refinement (Adkins, Boychuk, Remple, & Kleim, 2006; Kitago & Krakauer, 2013). To increase skill, a task must be challenging due to the complexity of the action, rather than the required muscle strength. Progression in the level of difficulty upon mastery results in improved learning and continued motivation (C. S. Green & Bavelier, 2008).

Skill learning occurs in multiple phases: an initial period of rapid improvement, followed by a consolidation period and continued improvement of the skill at a slower rate (Karni et al., 1998). Depending on the complexity of the task, skill mastery can take from several days to several years (Kitago & Krakauer, 2013; Nudo, Milliken, Jenkins, & Merzenich, 1996). One benefit of skill learning is that often, a learned skill remains producible following a period of no training. This indicates that there are long-term, experience-specific neural changes associated with skill learning, rendering the skill more resistant to detraining effects over time than strength training (Tyč, Boyadjian, & Devanne, 2005; Ungerleider, Doyon, & Karni, 2002).

It is known that the cortex plays an important role in swallowing and damage to the cortex can lead to dysphagia. Skill training is targeted to recruit cortical mechanisms to alter the

impaired response. Plasticity allows for reorganisation of neural regions to modify function and improve task performance (Bhatnagar, 2013; Kleim & Jones, 2008; Nudo, 2006b). This is evidenced by a larger cortical representation present in skilled individuals than novices (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995; Remple, Bruneau, VandenBerg, Goertzen, & Kleim, 2001). In patients with dysphagia, increased cortical representation of pharyngeal swallowing has been associated with recovery (Hamdy et al., 1998; Teismann et al., 2008).

As well as greater cortical activation, skill learning also helps individuals to modulate neurotransmitters, alters synaptic morphology and facilitates synaptogenesis (Adkins et al., 2006; Browne, Morley, & Parsons, 2012; Rioult-Pedotti, Friedman, Hess, & Donoghue, 1998). Rats trained in a skilled reaching task were found to have more synapses per neuron than untrained rats in the neural regions associated with the task in both the motor cortex and cerebellum (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990; Kleim et al., 2002; Kleim et al., 2004). Dendritic complexity relates to the number of dendritic branches; a greater number of branches results in greater synaptic connectivity, and therefore, greater potential for recovery. The length and complexity of dendrites has been shown to increase following skill training of both the unimpaired and the impaired limb in lesion studies (Allred & Jones, 2004; Biernaskie, Chernenko, & Corbett, 2004; T. A. Jones, Hawrylak, Klintsova, & Greenough, 1998). As the cortex has a modulatory role in swallowing, if skill training can adapt the cortical representation and neuronal structures associated with swallowing, it may be an approach that facilitates safe swallowing in patients with neurological damage or disease. However, transfer of the previously discussed limb and animal studies to swallowing skill training is not guaranteed and more research regarding neural adaptation as a result of swallowing skill training is required.

Plasticity may be adaptive or maladaptive (Humbert & German, 2013); it is therefore critical that treatment techniques target beneficial behaviours. Behavioural intervention following neurological injury is believed to be an effective contributor to adaptive plasticity (Nudo, 2006b). Several principles of neuroplasticity have been described, which provide information about how to maximise outcomes of skill training. These principles of neuroplasticity include use it or lose it, use it and improve it, experience specific, task repetition, task time, task specificity, task intensity, task salience, age, transference and interference (Robbins, Butler, et al., 2008). Four of the principles of neuroplasticity that are especially relevant to the

planning and implementation of swallowing skill training are the concepts of plasticity being experience specific, plasticity being dependent on the intensity of training, the importance of task salience and using and improving a skill. As plasticity is experience specific, it is important that the targeted task is a reflection of the behaviour that requires improvement. The cortical pathways associated with the task that is trained are likely to be the only pathways that are affected by practice (Nudo, 2006a). The intensity at which a task is performed is crucial as it is non-linearly related to neural change. Robbins and colleagues (2008) suggest that there is an intensity threshold that is necessary to induce changes to the neural substrates. When considering intensity of the sessions, it is also important to consider the structure of training, as continuous bursts of training are more beneficial for inducing neural change than intermittent training periods.

Practising and adapting a skill to refine motor movements is thought to increase neural representation when performing the task, this is related to the use it and improve it principle of neuroplasticity. Cortical neural plasticity is the intrinsic functional reorganisation of the cerebral cortex in response to new learning or retraining of a skill (Pascual-Leone, Amedi, Fregni, & Merabet, 2005; Tyč et al., 2005). For cortical change to occur the task cannot be a task that is performed optimally from the initial attempt; there must be the opportunity for skilled improvement with increasing task difficulty over time (Kleim, Barbay, & Nudo, 1998; Nudo et al., 1996; Perez, Lungholt, Nyborg, & Nielsen, 2004; Plautz, Milliken, & Nudo, 2000; Ungerleider et al., 2002). As swallowing is a concept that is often difficult for individuals to visualise and adapt, the topic of task salience is best address with the use of biofeedback. Biofeedback is discussed in greater detail below.

6.4.1 Biofeedback

The use of biofeedback has been researched since the 1940's, when it was found to enable participants to elicit change in processes that would otherwise not be considered to be under conscious control, such as their heart rate and blood flow (McKee, 2008). As swallowing is an abstract concept, it likely falls into this group of processes. Biofeedback may the patient to visualise minute changes to swallowing timing or intensity, allowing increased conscious control. Importantly, it is not only the patient who is able to visualise their swallowing but also the clinician. Biofeedback allows for specific feedback into the areas of swallowing that require adaptation to perform the task precisely. Biofeedback can increase the salience of a task as it can make an abstract task more concrete. Tasks that are purposeful and related to

the movement that is being trained facilitate neural reorganisation (Robbins, Butler, et al., 2008). For successful biofeedback, the feedback must be simple to understand, to allow modifications to occur in real time. To ensure that the feedback is easy to understand, it is usually presented in an auditory or visual modality.

The uses of biofeedback have expanded with the invention of new instrumentation, allowing an increase in the number of physiologic processes to be visualised and altered. Early research into biofeedback modalities for swallowing investigated the use of VFSS (Logemann & Kahrilas, 1990), sEMG (Bryant, 1991) and videoendoscopy (Denk & Kaider, 1997). These studies highlighted the benefits of biofeedback in providing objective information to increase a patient's comprehension and expectations of therapy tasks, to improve outcomes, especially during the early learning phase. However, limitations were also acknowledged. Feedback from VFSS was time restricted due to the need for ionising radiation (Logemann & Kahrilas, 1990). Discomfort associated with invasive endoscopic methods of biofeedback resulted in several cases of early cessation of treatment (Denk & Kaider, 1997). These early studies demonstrated the potential positive effects of biofeedback for swallowing and highlighted the need for further investigation.

Since these early studies, research has investigated various alternative methods for providing biofeedback to patients. Measurement of lingual pressure is a non-invasive method of providing biofeedback to patients regarding the force produced during by the lingual muscles. In a series of two studies, Svensson and colleagues investigated the potential for a lingual training task with biofeedback to induce cortical plasticity (Svensson, Romaniello, Arendt-Nielsen, & Sessle, 2003; Svensson, Romaniello, Wang, Arendt-Nielsen, & Sessle, 2006). Healthy participants completed a training protocol during which they protruded their tongue against a transducer that measured force. Participants were instructed to produce exactly one Newton of force on the transducer. It is likely that changes as a result of this task were due to skill, and not strength, as one Newton is only 3 – 18% of what would be expected during a maximal tongue protrusion task (Blumen et al., 2002; Sha, England, Parisi, & Strobel, 2000). Following only one hour of training, participants demonstrated evidence of neuroplasticity, with increased excitability in the primary motor cortex (Svensson et al., 2003; Svensson et al., 2006). This highlights the potential for neuroplasticity as a result of bulbar skill training. Further research investigated transference of lingual skill training to functional outcomes in dysphagic patients. Patients in this study participated in 24 sessions of a combination of

lingual strength and skill training protocol (Steele et al., 2013). This training regime resulted in increased lingual pressure, improved accuracy of lingual pressure generation, reduced airway invasion and improved bolus control. However, as training included aspects of increasing strength as well as skill, the observed improvements cannot be attributed to skill training alone.

Respiratory swallow training has been investigated as a method of skill training to improve swallowing outcomes in patients with dysphagia due to head and neck cancer (Martin-Harris et al., 2015), Parkinson's disease (J. A. Curtis, Dakin, & Troche, 2020) and anoxic brain injury (J. A. Curtis, Seikaly, & Troche, 2020). In 30 patients with head and neck cancer, respiratory phase and volume during swallowing was visualised using nasal airflow and signals from the rib cage and abdomen (Martin-Harris et al., 2015). The targeted swallowing behaviour was swallowing mid-expiration with a mid to low lung volume. The treatment protocol was split into three training modules: identification, acquisition and mastery. Progression through the levels was dependent on the participant achieving success at the previous level and training continued until the participant achieved success at all levels. During the identification phase, participants identified the target respiratory pattern and lung volume on simulated tracings and while swallowing. During the acquisition phase, participants aimed to complete the target swallowing pattern with a bolus with biofeedback. For the mastery phase, participants aimed to complete the target swallowing pattern with a bolus but without biofeedback. All patients were able to master the task within eight sessions. Significant improvement in laryngeal vestibule closure, tongue base retraction, pharyngeal residue and airway invasion were noted post treatment with maintenance of improvement at one-month post-treatment. The improvements in untrained aspects of swallowing, such as tongue base retraction, indicate transference of the learned skill to other aspects of swallowing. In single case studies in patients with Parkinson's disease and anoxic brain injury, improvements in respiratory swallow coordination, airway invasion and pharyngeal residue were observed following training of respiratory swallow coordination with clinician feedback but without the use of biofeedback (J. A. Curtis, Dakin, et al., 2020; J. A. Curtis, Seikaly, et al., 2020). Swallowing pattern without biofeedback may be observable by the clinician but further research is necessary to investigate accuracy of clinician feedback in the absence of biofeedback and differences in learning effects for patients with and without direct biofeedback.

Huckabee, Lamvik, and Jones (2014) identified a group of 16 patients with dysphagia that was characteristic of mis-sequencing of pharyngeal contraction. Low-resolution pharyngeal manometry provided visualisation of the deficit to the patients. Participants were instructed to increase the temporal separation between contractile waves produced by the proximal and distal pharynx. Following twice-daily treatment sessions for a minimum of one week, patients achieved success at the task. The average time between peak pressure in the proximal and distal pharynx increased from 15 ms to 137 ms. As a result, 11 patients were able to return to a full oral diet following treatment and subjectively reported reduced nasal redirection. However, these findings were not confirmed with instrumental assessment and further research including VFSS post-treatment would be beneficial. Importantly, patients in this group demonstrated effective learning when modulating the pharyngeal phase of swallowing in a task that, without the use of biofeedback, would likely be impossible for the clinician to explain, provide feedback of success or measure progress.

Biofeedback in Strength and Skill Training (BiSSkiT) is a software-enabled training protocol that uses submental sEMG to provide biofeedback of timing and amplitude of muscle activation. During the skill training protocol, individuals swallow such that the peak of the sEMG waveform lands within a target box. The target box is randomly placed on the screen to increase variability in the timing and amplitude of swallowing. The size of the box varies to make the task easier or more difficult depending on levels of success. A small pilot study investigated the effects of skill training using the BiSSkiT software for patients with Parkinson's disease. Ten participants completed two weeks of daily skill training with 100 swallows per session. Following two weeks of skill training, improvement in swallowing efficiency (TWST) and quality of life (Swal-QOL) scores, and a reduction in lingual movements prior to swallowing onset were observed, demonstrating transference of the trained task to functional swallowing (Athukorala, Jones, Sella, & Huckabee, 2014). These improvements were maintained across a two-week no-treatment phase, indicating skill retention. However, there were no instrumental assessments completed to determine if changes in swallowing safety or biomechanics occurred. In a further case study of a patient with multiple system atrophy, six sessions of skill training with the BiSSkiT software, with a modified home practice task resulted in increased swallowing safety as indicated on FEES (S. E. Perry, Sevitz, Curtis, Kuo, & Troche, 2018). Further research is necessary to determine the appropriate intensity of skill training and the additional effects of home-based tasks without biofeedback. However, these early studies demonstrate the potential for maintenance or

improvement in swallowing function in patients with neurodegenerative disease as a result of skill training.

6.4.2 Skill training for individuals with MND

Neuroplasticity is a critical aspect of skill training, and it is therefore important to consider whether neuroplasticity is possible for patients with this rapidly degenerative disease that is neurological in origin. Early research in limb literature identified a difference in neural activation between individuals with MND and healthy controls when performing a simple motor task (Konrad et al., 2002; Konrad et al., 2006; Schoenfeld et al., 2005). During a simple hand movement task, individuals with MND demonstrated greater activation in areas of the brain that are involved in higher level motor tasks and motor planning than control subjects (Konrad et al., 2002; Stanton et al., 2007). Individuals with weakness due to peripheral lesions were compared to the patients with MND. The weakness matched controls did not demonstrate the same increases in cortical activation as was seen in the MND patients, indicating that the neural change was not a result of muscle weakness or task difficulty, but exclusive to those with weakness secondary to MND (Stanton et al., 2007).

Mohammadi, Kollewe, Samii, Dengler, and Münte (2011) propose two distinct phases of neuroplastic change in individuals with MND when performing limb motor tasks. These phases consist of: 1) an initial phase of increased cortical activation associated with maintained function and 2) a later phase in which further loss of motor neurons occurs with concomitant reduction in strength. To investigate this, 22 participants were divided into three groups depending on hand weakness: no weakness (n = 11), mild weakness (n = 17) or marked weakness (n = 19). Participants were included in multiple groups as their function declined. FMRI was used to gather information about neural activation during a finger flexion and extension task with the right hand. As in previous research, patients in the no weakness group demonstrated an increase in areas of neural activation during the task compared to healthy controls. In patients with mild and marked weakness the activated area was the same as the ALS patients with no weakness; however, there was evidence of progressive decline in percent signal change. The authors suggest that this may be due to progressive loss of pyramidal cells. The first proposed phase of neuroplastic change was during the time in which no weakness was observed in the limb, but the size of the sensorimotor cluster in the ipsilateral region was increased compared to healthy controls. Further research has also demonstrated increased activation in the primary motor cortex, and

supplementary motor areas during limb tasks, suggesting that neural changes in the early phase are a result of compensatory cortical plasticity (Konrad et al., 2002; Schoenfeld et al., 2005; Shen et al., 2015). As muscle strength decreased, mean signal change and beta weights decreased, indicating decreased neural activity compared to those with no weakness. This indicates that weakness may occur as a result of further loss of motor neurons and inability to further compensate by recruiting additional cortical regions.

There is speculation that the presence of cortical reorganisation in response to neurodegeneration differs between spinal and bulbar tasks. Although increased cortical activation has been observed in patients with MND during hand movement tasks, Kollewe et al. (2010) found reduced cortical activation in patients with MND when performing a vertical tongue movement task. Twenty patients with MND and healthy age matched controls were recruited. Patients were separated into groups based on the presence of bulbar function and hand muscle weakness. The presence of bulbar symptoms was based on the bulbar function section of the ALSFRS-R; however, it is not stated what the cut-off was for the patients in the "showed bulbar signs" group. The grouping for muscle strength was based on the Medical Research Council Scale for testing muscle strength in patients with radial palsy (Paternostro-Sluga et al., 2008), which split patients into three groups based on severity of muscle weakness of the hand. The task consisted of either right hand movements or vertical tongue movements during fMRI. Four blocks of 20 seconds of task performance were performed, with each block followed by 20 seconds of rest. As in previous research, patients with no muscle atrophy of the right hand demonstrated increased cortical activation compared to healthy controls during the finger flexion task. However, during the lingual task, patients with no bulbar symptoms did not demonstrate a significant change in cortical activation compared to healthy controls, but those with bulbar symptoms demonstrated decreased cortical activation. The authors concluded that "this suggests that neurodegeneration of the bulbar system cannot be compensated and may explain the faster progress of the bulbar-onset form of ALS" (Kollewe et al., 2010, p. 808). However, there are limitations to this study. The separation of patients into bulbar symptoms and no bulbar symptoms was not specific as the ALSFRS-R investigates changes to functional activity rather than muscle weakness. This means that a patient could be experiencing muscle weakness in the absence of functional change and placed within the no bulbar symptoms group. Further, unlike finger flexion which is commonly used to grasp items, vertical tongue movements are not a functional task and it

is possible that patients do not perform this task frequently enough to induce compensatory neuroplasticity in response to subtle changes in task performance.

Further research has investigated cortical activation during swallowing in patients with MND compared to healthy controls with the use of functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) (Li et al., 2009; Teismann et al., 2011). Li and colleagues (2009) used FEES to identifying dysphagia in patients. Interestingly, both Li et al. (2009) and Teismann et al. (2011) demonstrated a hemispheric shift, with greater activation of the right hemisphere when compared to the left in patients with dysphagia. Teismann et al. (2011) hypothesised that this was due to increased resources being provided to the pharyngeal phase of swallowing, under the assumption that this phase is right hemisphere dominant. However, as previously discussed, there is conflicting evidence in the literature regarding hemispheric dominance for different phases of swallowing. In an fMRI study in which participants completed saliva swallows, Li et al. (2009) demonstrated bilateral increased activation in the sensorimotor cortex for patients with MND without dysphagia compared to healthy controls, indicating functional neural reorganisation to prolong safe and efficient swallowing. When compared to healthy controls, reduced cortical activation during swallowing was observed for MND patients with mild dysphagia and further reduction in those with severe dysphagia (Li et al., 2009; Teismann et al., 2011). These findings align with the phases of neuroplasticity proposed by Mohammadi et al. (2011).

Cortical reorganisation has been demonstrated in patients with MND for limb and functional swallowing tasks prior to the presence of functional decline (Konrad et al., 2002; Konrad et al., 2006; Li et al., 2009; Schoenfeld et al., 2005). Increased cortical excitement in response to early motor changes in MND demonstrate the potential for neural adaptation to occur in patients with this neurogenic disease. As previously discussed, in the limb literature skill training has been linked to increased corticomotor excitability, neuroplasticity and functional improvement (J. L. Jensen et al., 2005; Remple et al., 2001). However, to date, the potential for skill training to further facilitate the observed spontaneous changes in MND has not been investigated. It is possible that with the addition of skill training and visual feedback, increased plasticity may be facilitated, with the potential for improvement or maintenance of function.

One recent study investigated skill training with biofeedback in patients with MND. In a non-randomised controlled trial, J. Tomik et al. (2020) investigated the use of low resolution

oesophageal manometry as biofeedback to improve dysphagia. This study recruited 20 participants with MND, 10 of whom agreed to participate in treatment. Patients in the treatment group participated in five sessions of biofeedback training, with a five-day break between each session. During treatment, patients were taught about primary, secondary and non-peristaltic oesophageal contractions and oriented to their swallows displayed on a screen. Ten bread and ten liquid swallows were completed per treatment session; however, further information about the training protocol and feedback provided by the researcher during training is not discussed in the journal article. There was no assessment session immediately following treatment to determine the presence of immediate treatment effects or success in task learning during the treatment protocol. One year following treatment, patients who underwent skill training demonstrated a significant increase in primary peristaltic wave frequency (the peristaltic waves initiated in response to swallowing and provide the main force for bolus propulsion). Patients who underwent skill training also demonstrated a reduction in non-peristaltic waves (oesophageal waves in which no peristaltic wave occurs in the distal smooth muscle oesophagus after proximal oesophageal peristalsis and indicate abnormalities in oesophageal peristalsis). No significant changes in these outcomes were observed in the control group. BMI was also monitored, with less decline in BMI in the treatment group compared to the control group. A reduction in decline of BMI may indicate improved nutritional outcomes; however, there are other factors that may contribute to BMI including muscle wasting, which is common in patients with MND. There were significant limitations to this study. Patients were not randomised to a group, the patients who agreed to treatment are the patients who underwent the treatment. This could have created a bias, with patients in the treatment group being those who are more proactive and involved in their care or those with fewer symptoms making it easier to get to the treatment sessions. Information about group differences between the treatment and control group are not provided, including time since diagnosis, severity of dysphagia and symptom onset type. It may, therefore, be possible that there are unreported inherent differences between groups that account for the observed changes. Finally, immediate treatment effects are not reported. It is therefore, difficult to conclude that the observed differences are a result of the treatment. Definitive conclusions about the effectiveness of the treatment protocol cannot be gleaned from the reported outcomes. Further research investigating skill training for patients with MND to improve swallowing and nutritional outcomes would be beneficial to determine if the positive outcomes in the treatment group can be attributed to skill training. It would be imperative that

this research investigate changes immediately following training in addition to longer term follow-up.

7. Summary of evidence

Dysphagia presents in 86% to 98% of patients with the corticobulbar subtype of MND, and in approximately 73% of patients with the corticospinal subtype (A. Chen & Garrett, 2005; Kühnlein et al., 2008; Onesti et al., 2017). Both the oral and pharyngeal phases of swallowing are affected, with resulting negative impacts on quality of life and survival (Burkhardt et al., 2017; Paris et al., 2013; Tabor et al., 2016). Common clinical methods of managing dysphagia include diet modification and postural adaptations; however, these strategies do not alter the course of dysphagia progression and can negatively impact quality of life.

Although historically avoided in this population, short term beneficial effects of mild to moderate intensity strength training have been demonstrated in the limb and respiratory literature (Plowman, 2015). To date, little research has been conducted investigating the optimal intensity of swallowing treatment and there are no clinically friendly methods of identifying fatigue of bulbar muscles during exercise. It would be of benefit to investigate a non-invasive and simple to use method of quantifying muscle fatigue to ensure that treatment is at an appropriate intensity for patients with MND to optimise training intensity without producing harmful levels of fatigue.

Expiratory muscle strength training (EMST) has been investigated in patients with MND. Increased maximum expiratory pressure and potential improvements in swallowing physiology have been demonstrated as a result of treatment (Plowman et al., 2019; Plowman, Watts, Tabor, et al., 2016). However, the improvement in swallowing was not compelling and more research with a large sample size and continuous outcome measures is necessary to further investigate this. The resistance set during this task was reduced to 50% of a participant's maximum expiratory pressure to ensure that training was not at an intensity that could cause harm. This is less than the minimum recommendations made in sport and exercise science for training to be greater than 60% of an individual's one rep maximum and far below the reported ideal of 70-85% of one repetition maximum for muscle hypertrophy (Burkhead et al., 2007; Porter, 2000; Wernbom et al., 2007). This may have contributed to the limited transference of effects from EMST task to swallowing but may be necessary in this population. Long term outcomes of EMST have not been investigated; however, other

forms of strength training in MND have demonstrated a detraining effect following the offset of treatment (Cheah et al., 2009; A. C. Pinto et al., 1999). Because of these limitations, strength training may not be the most appropriate form of dysphagia treatment for patients with MND.

Skill training is an alternative form of treatment that is emerging in the dysphagia literature. In the limb literature, successful skill training has been shown to result in increased neuroplasticity and cortical excitability associated with the trained task (J. L. Jensen et al., 2005; Remple et al., 2001). In patients with Parkinson's Disease, a skill training protocol using sEMG hardware and BiSSkiT software for biofeedback of submental muscle activation during swallowing was found to have beneficial effects on both functional swallowing outcomes and quality of life following two weeks of daily treatment (Athukorala et al., 2014). As dysphagia is also progressive and neurological in origin for patients with MND, it is reasonable to hypothesise that functional swallowing improvement may be observed in this patient group. However, the use of skill training to enhance neural functioning has not been assessed in patients with MND and it therefore remains unknown if plasticity can be elicited through behavioural changes. Evidence of increased cortical recruitment during swallowing exists in this population prior to functional decline (Li et al., 2009). However, with progressive neural degeneration over the course of the disease progression, cortical recruitment decreases and functional decline occurs. It has not yet been investigated whether skill training can facilitate a prolonged period of cortical plasticity, leading to improved functional outcomes in this population. Investigation of BiSSKiT at a mild to moderate intensity in patients with MND would be a valuable first step in understanding the potential effects of skill training for patients with this neurodegenerative disease.

PART II: EXPERIMENTAL STUDIES

8. Objectives and Hypotheses

8.1 Fatigue of submental muscles during a lingual endurance task in healthy participants

8.1.1 Research question

Does average sEMG output reflect bulbar muscle fatigue during a lingual pressure task?

8.1.2 Objective

To determine whether simple sEMG amplitude can be used to indicate muscle fatigue during a lingual endurance task.

8.1.3 Hypotheses

1. The endurance time of a sustained lingual press at 50% maximum capacity will decrease in the final trial compared to the initial trial as a result of fatigue.
2. Area under the curve when adjusted for time will increase in the final trial compared to the initial trial as a result of fatigue.

8.1.4 Rationale

Fatigue is expected to occur during isometric contractions that are greater than 30% of an individual's maximum voluntary contraction (De Luca, 1997). As the maximal lingual endurance task is set at 50% of an individual's maximum voluntary contraction, fatigue is expected. As muscles fatigue, additional motor units are recruited, firing frequency increases and discharges are synchronised to sustain the force produced. Electromyography of a fatiguing muscle with a stable force output should reflect muscle fatigue with an increase in amplitude of the waveform (Chang et al., 2016).

8.1.5 Significance

An assessment of fatigue of bulbar muscles would help in the development of exercise programmes for patients with MND as it is recommended that exercise is targeted at a mild to moderate intensity. If exercise programmes can be tailored and implemented at an intensity that is shown to be mild to moderate for an individual, dependent on their personal fatigue levels, this may help to reduce adverse effects associated with high intensity exercise, and

therefore, increase ability to offer safe treatment options to patients. Current methods of quantifying fatigue are invasive or involve complex equipment and algorithms, which are not often clinically accessible. This methodological study is an important first step in developing a simple, non-invasive quantitative assessment for fatigue of bulbar muscles.

8.1.6 Proposed study

Twenty-four healthy participants will be recruited with three males and three females in each of the following age groups: 20-39, 40-59, 60-79 and over 80. Each participant will complete eight repetitions of a maximum lingual endurance task. The lingual endurance task will be completed at 50% of an individual's pre-determined maximum pressure. During each trial, participants will press the anterior surface of their tongue against a lingual pressure bulb with concurrent sEMG over the submental muscles to measure muscle activity. Outcome measures will be the time that a lingual endurance trial is sustained and the average sEMG output. Linear mixed effects models will be used to investigate the effect of fatigue over trials on the outcome measures.

8.2 Pilot study investigating the feasibility of skill training for patients with dysphagia secondary to MND

8.2.1 Research questions

- Is skill training for swallowing a feasible treatment option for patients with MND?
- Would it be feasible to perform a larger scale treatment study in patients with MND in Christchurch, NZ?

8.2.2 Objectives

- To determine the feasibility of participating in a skill-based swallowing task with surface electromyography as biofeedback in patients with dysphagia secondary to MND.
- To determine if skill training results in potential improvement in swallowing outcomes and quality of life for patients with MND, indicating the need for further research.
- To investigate rates of recruitment to determine the feasibility of conducting a large-scale treatment efficacy study with patients with MND in Christchurch.

8.2.3 Hypotheses

- Participants will be able to participate in skill training with surface electromyography as biofeedback as evidenced by the participants completing 80 swallows per session and a drop-out rate less than 10%.
- Participants will demonstrate improvement in functional swallowing outcomes as evidenced by:
    - Increased volume per swallow at the end of the treatment period compared to baseline as measured by the TWST
    - Decreased time per swallow at the end of the treatment period compared to baseline as measured by the TWST
    - Increased volume per sec at the end of the treatment period compared to baseline as measured by the TWST
    - Decreased time to complete the TOMASS following treatment compared to baseline.
    - Decreased number of swallows to complete the TOMASS following treatment compared to baseline.
- Participants will demonstrate improvement in quality of life as evidenced by:
    - Increase in swallowing related quality of life total score following treatment compared to baseline as measured by the Swal-QOL.
    - Decrease in EAT-10 score following treatment compared to baseline.
- Participants will demonstrate improvement on speech related outcomes as demonstrated by:
    - An increase in syllable repetition following treatment compared to pre-treatment
    - An increase in prolonged vowel duration following the treatment period when compared to the pre-treatment assessment.
- Improvements in functional swallowing ability, quality of life and speech outcomes will be maintained over the follow-up period.

8.2.4 Rationale

It is hypothesised that participants will be able to participate in this study as sEMG treatment has no known side effects and this protocol will be presented at an intensity that is not likely to result in muscular fatigue. For patients with MND, low to moderate intensity exercise is

recommended as high intensity exercise may cause fatigue and increase the rate of functional decline (Carreras et al., 2010; Plowman, 2015). As targets are placed between 40% and 70% of a patient's maximal contraction, skill training using the BiSSkiT software is likely to fall within the mild to moderate intensity category. For patients with MND and no evidence of dysphagia, cortical activation is increased during swallowing compared to healthy controls, likely as a result of compensatory plasticity (Li et al., 2009). Skill training using the BiSSKiT software is a swallowing specific task with the potential to increase positive neuroplasticity with transference of skill to functional swallowing outcomes in patients with neurodegenerative diseases (Athukorala et al., 2014; S. E. Perry et al., 2018).

8.2.5 Significance

As no previous research has been conducted using skill training for swallowing outcomes in patients with MND, this pilot study is a necessary first step to determine the relevance of further research.

8.2.6 Proposed study

This pilot study aims to recruit six to ten participants in the Christchurch region. If recruitment within Christchurch is not possible, recruitment will expand to include other centres within NZ. Participants will undergo four weeks of skill training for swallowing using the BiSSkiT software. These four weeks of active treatment will be preceded by a four-week period of no treatment to assess natural decline and followed by a four-week period of no treatment to assess maintenance effects. Functional swallowing will be assessed by the TOMASS and TWST, and patient perception of impairment by the Swal-QOL and EAT-10. Speech outcomes will be assessed by vowel prolongation, alternating motion rate and sequential motion rate. Due to the small number of participants, descriptive statistics will be used to describe observed changes in outcome measures.

8.3 Exploratory study investigating the effects of skill training on swallowing and quality of life in patients with MND

8.3.1 Research question

Does skill training for swallowing improve swallowing and quality of life outcomes for patients with MND?

8.3.2 Objective

To determine if a two-week skill training protocol is beneficial for swallowing and quality of life outcomes for individuals with MND.

8.3.3 Hypotheses

- Participants will increase temporal accuracy in the treatment task over the treatment period.
- Participants will increase amplitude accuracy in the treatment task over the treatment period.
- Swallowing skill will be maintained over the follow-up period.
- Participants will demonstrate a reduction in the rate of decline in swallowing related quality of life over the treatment period when compared to the baseline period. This will be demonstrated by:
    - Reduced rate of decline in total swallowing symptom frequency as measured by the Swal-QOL
    - Reduced rate of decline in pharyngeal symptom frequency as measured by the Swal-QOL
- Improvements in swallowing related quality of life will be maintained over the follow-up period.
- Participants will demonstrate increased speed of swallowing initiation on VFSS following treatment compared to the baseline period as demonstrated by a decrease in OPTT. This will be observed for:
    - Five cc water boluses
    - Five cc puree boluses
    - Boluses of a bite of cracker
- Participants will demonstrate an increased speed of pharyngeal bolus transit following treatment when compared to pre-treatment as measured by
    - Decreased HPTT with 5 cc water boluses measured by VFSS
    - Decreased HPTT with 5 cc puree boluses measured by VFSS
    - Decreased HPTT with a bite of cracker measured by VFSS
    - Decreased TPTT with 5 cc water boluses measured by VFSS
    - Decreased TPTT with 5 cc puree boluses measured by VFSS
    - Decreased TPTT with a bite of cracker measured by VFSS

    - Decreased hypopharyngeal bolus presence time with 5cc saline boluses measured by HRIM
    - Decreased hypopharyngeal bolus presence time with 5cc puree boluses measured by HRIM
- Improvements in swallowing timing will be maintained over the follow-up period.
- Participants will demonstrate a reduction in rate of decline in pharyngeal pressure generation over the treatment period when compared to the baseline period for:
    - Pharyngeal constriction ratio (PCR) of five cc water boluses measured by VFSS
    - PCR of five cc puree boluses measured by VFSS
    - PCR of a bite of cracker measured by VFSS
    - Hypopharyngeal peak pressure (PeakP) measured by HRIM for 5 cc thin liquid boluses
    - Hypopharyngeal peak pressure (PeakP) measured by HRIM for 5 cc puree boluses
- Participants will demonstrate a decrease in rate of decline in extent of UES opening measured by VFSS over the treatment period when compared to the baseline period for:
    - Five cc water boluses
    - Five cc puree boluses
    - Boluses of a bite of cracker
- Participants will demonstrate an increase in hyoid excursion measured by VFSS following treatment compared to pre-treatment for:
    - Five cc water boluses
    - Five cc puree boluses
    - Boluses of a bite of cracker
- Participants will demonstrate an increase in hyoid excursion measured by US following treatment compared to pre-treatment for:
    - Five cc water boluses
    - Five cc puree boluses
    - Dry swallows
- Participants will demonstrate improvement in functional swallowing outcomes over the treatment period compared to the baseline period as demonstrated by:

- Decreased number of swallows measured by the TOMASS
- Increased volume per swallow measured by the TWST
- Decreased time per swallow measured by the TWST
- Increased volume per sec measured by the TWST

- There will be no significant muscle hypertrophy over the treatment period as measured by CSA of the geniohyoid^{+} muscle complex (GH^{+}), and anterior belly of the digastric muscles.

8.3.4 Rationale

Improvements in functional swallowing outcomes were observed in the pilot study for patients with mild to moderate dysphagia. These signs of improvement suggested that further research would be beneficial to investigate the physiology associated with functional changes. Many outcome measures will be assessed as the research is exploratory.
It was hypothesised that no significant muscle hypertrophy would be observed as peripheral muscle hypertrophy occurs as a result of exercises that are conducted above the habitual level (Rasch & Morehouse, 1957; Zatsiorsky & Kraemer, 2006) and the skill training protocol will occur at 30 – 70% of an individual's effortful swallow, which is within the range of normal swallowing.

8.3.5 Significance

Treatment options are currently limited for patients with MND due to the historical belief that exercise would result in negative outcomes for this patient group. With emerging evidence that exercise may be beneficial for patients at a mild to moderate intensity, it is crucial that various options for this group are investigated. Effective swallowing treatment for patients with MND could increase life expectancy and quality of life by prolonging the time patients are able to eat orally and by reducing sequelae associated with dysphagia that can result in mortality such as malnutrition and aspiration pneumonia.

8.3.6 Proposed study

Twenty-four patients with dysphagia secondary to MND will be recruited across sites in NZ (Auckland and Christchurch) and the USA (New York City). The study will be an A-B-A trial with a baseline period, treatment period and follow-up period, each two weeks. During the treatment period, individuals will participate in a two-week skill training protocol using

sEMG as biofeedback through the BiSSkiT software. For all participants, quality of life will be assessed with the Swal-QOL questionnaire and swallowing will be assessed by the TOMASS, TWST, and Ultrasound. To provide more information about swallowing physiology and how this is affected by a period of skill training, participants in Auckland will additionally undergo VFSS and participants in Christchurch will additionally undergo VFSS and HRIM. Data will be analysed using linear mixed effects models to determine if there is a difference between each of the assessment points and to compare the amount of change across each of the periods.

9. Fatigue of submental muscles during a lingual endurance task in healthy participants[1]

9.1 Introduction

Research has demonstrated that while mild to moderate exercise may be beneficial for patients with MND, high intensity exercise has been reported to be detrimental (Carreras et al., 2010; Plowman, 2015). This theory is based on the premise that high intensity exercise leads to fatigue of bulbar muscles and a faster rate of decline. However, degree of muscle fatigue as a result of the exercise was not documented during these studies. More information about muscle fatigue of patients with MND during exercise may help to increase understanding of the mechanism that results in poorer outcomes for patients following high intensity exercise and to individualise exercise regimes.

Mechanisms of muscle fatigue are dependent on the type, intensity and frequency of exercise, and demographic factors such as age, sex, degree of general fatigue and health status. This includes a faster rate of muscular fatigue during isometric limb tasks in patients with MND compared to healthy controls (Finsterer & Drory, 2016; Palacios et al., 2015; M Sanjak et al., 2004; Sharma & Miller, 1996; Skurvydas et al., 2006). As there are many factors contributing to degree of muscular fatigue, it would be beneficial to tailor treatment programmes to an intensity that is the appropriate level by quantifying fatigue in an individual. However, a clinically applicable method of determining levels of bulbar muscle fatigue is not currently available. There are many biological and mechanical methods for measuring muscle fatigue, including measuring lactic acid build up, force produced and muscle activity through EMG (Finsterer & Drory, 2016). These have been used in limb muscles to quantify fatigue during and following different exercise regimes (Al-Mulla, Sepulveda, & Colley, 2012).

The most common non-invasive method for assessing muscular fatigue is sEMG (Al-Mulla et al., 2012). Benefits of using sEMG to measure muscle fatigue are that it can measure muscle activity as the task is performed and it has been found to be correlated with both biochemical

[1] This study is somewhat peripheral, but related, to the scope of the overall thesis. It was designed as a community school engagement project to introduce two 13 year old high school students to research methods. The students were tutored in research methods and assisted with participant recruitment, data collection and simple preliminary data analyses.

and physiological muscle changes associated with the fatiguing process (Cifrek, Medved, Tonković, & Ostojić, 2009; del Toro et al., 2019). SEMG works by measuring the activity of motor units. When muscles become fatigued, additional motor units are recruited, firing frequency increases and discharges are synchronised to produce continual power output at a stable level; this is reflected in sEMG output. SEMG is not specific to one muscle, it detects signals from all nearby muscles with motor units that are closer to the electrode producing a higher amplitude waveform than those that are further away (Stepp, 2012). Therefore, sEMG is best at providing information about the activation of superficial muscles.

Mean and median frequency are the gold-standard for measuring fatigue using sEMG; a decrease in frequency indicates fatigue (Al-Mulla et al., 2012; Phinyomark, Thongpanja, Hu, Phukpattaranont, & Limsakul, 2012). Measurement of fatigue using sEMG analysis of the submental muscles has been used to compare levels of muscle fatigue between the head lift exercise and chin tuck against resistance (CTAR) (Sze et al., 2016). Fatigue was assessed using maximum muscle activation, frequency values and recurrence values. This method of assessment differentiated the levels of fatigue between the two exercises, demonstrating that although submental muscle activation was similar, the level of fatigue of the sternocleidomastoid muscles was greater during the head lift exercise than CTAR. However, there was a large confounding variable with this method of fatigue analysis as there was contact between the sEMG electrodes and the ball used for the exercise. Further investigation of methods for identifying levels of fatigue of bulbar muscle fatigue is required. However, it is important that note that although frequency measurements are the gold standard, access to measures of frequency is not always achievable from basic equipment without the use of complex algorithms, making them difficult to access in clinical situations.

Root mean square (RMS) is a measure of the square root of the average voltage measured by sEMG for a given period of time. It creates a smooth waveform that allows sEMG data to be easily interpreted and is a common method for smoothing the waveform. An alternative smoothing method is to rectify and filter the raw data. These processes allow the sEMG data to be easily interpreted. When the power output produced by the muscle remains stable, an increase in sEMG amplitude is expected as fatigue increases (Chang et al., 2016). Therefore, following smoothing, sEMG amplitude may be used as another method for identification of muscular fatigue. One of the disadvantages of using an average sEMG amplitude is that a change in power produced by the muscle will also influence the amplitude. This limits the use

of this strategy in maximum pressure trials as force usually decreases as fatigue increases (Chang et al., 2016). However, fatigue is expected to be observed via average amplitude when a constant force is generated by isometric muscle contraction that is greater than 30% of an individual's maximum voluntary contraction (De Luca, 1997). Calculating an average amplitude from sEMG output during a sustained isometric task can be achieved with basic equipment that provides a rectified and filtered time by amplitude waveform of sEMG. This method may, therefore, be more accessible for clinicians and it would be valuable to determine whether using average amplitude is an effective method of measuring fatigue of submental muscles.

This study aims to investigate if average submental sEMG output that has been smoothed and filtered will increase as a result of fatigue over multiple trials of a lingual endurance task. As the submental muscles are known to be recruited during a tongue to palate press task (P. M. Palmer et al., 2008), one might expect that these muscles would become fatigued during a repeated 50% of maximum isometric pressure (MIP) lingual endurance task. It is hypothesised that this would be reflected by a decrease in lingual endurance time and an increase in average sEMG amplitude.

9.2 Methods

9.2.1 Participants

Twenty-four healthy participants were recruited with three men and three women in each of the following age bands: 20-39, 40-59, 60-79 and 80+. Participants were recruited through convenience sampling from the general population via written and verbal advertisements. No participant reported a history of muscular or neurological conditions or swallowing impairment. Informed consent was gained prior to participation. Ethical approval for this study was granted through the University of Canterbury Human Ethics Committee.

9.2.2 Materials

The KayPentax Digital Swallowing Workstation (KayPentax, Lincoln Park, NJ, USA) was used to collect and display both lingual pressure and sEMG data. A three-sensor pressure bulb was modified to contain only one air-filled bulb to measure lingual pressure. During the task, lingual pressure was displayed as a time (secs) by pressure (mmHg) waveform on the monitor (figure 9.1). Single channel sEMG was used with Triode^{TM} silver-silver chloride

electrodes with 2 cm spacing secured with an adhesive patch (Thought Technology Ltd., Canada). Raw sEMG signals were sampled at 250 Hz, bandpass filtered (50 – 250 Hz), integrated (50ms time constant), and rectified. The resulting signal was display as a time (secs) by amplitude (µV) waveform (figure 9.1).

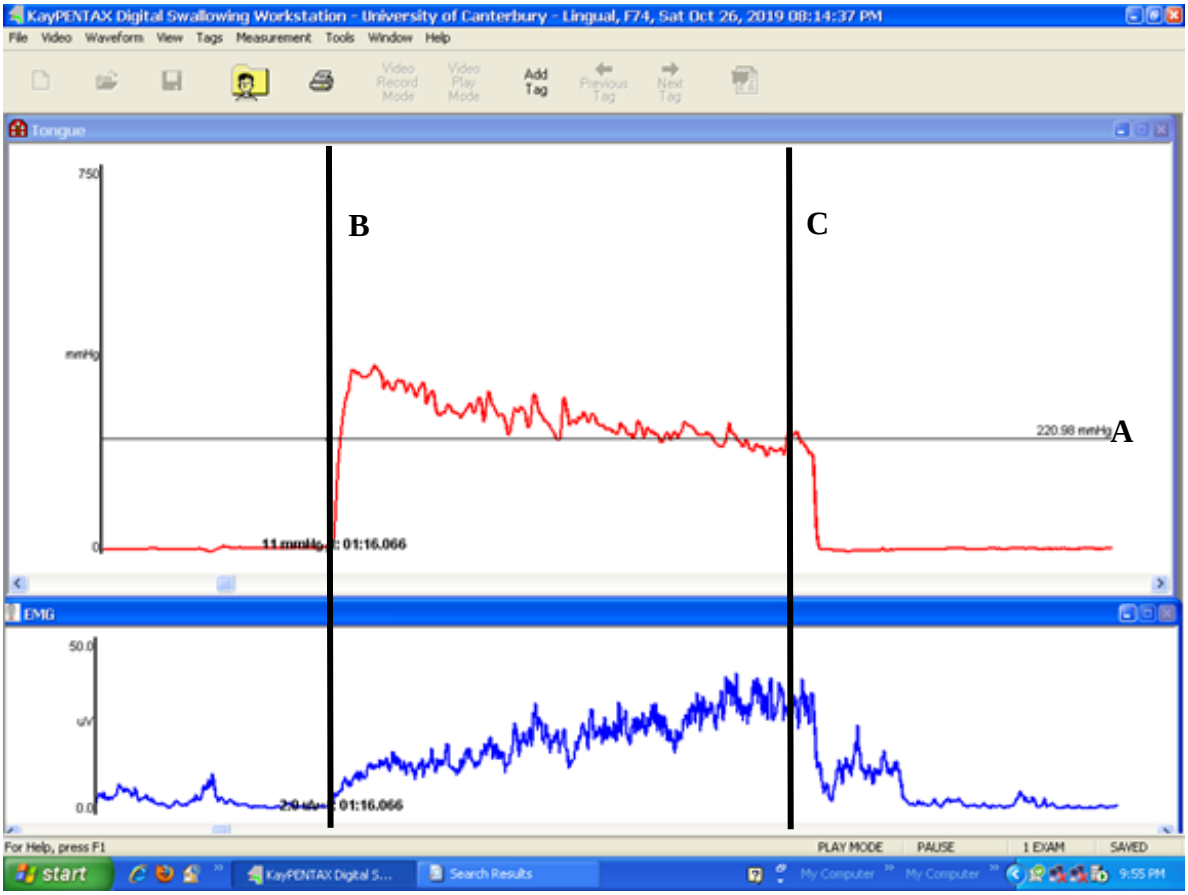

Figure 9.1. Monitor viewed by participants. Red line represents lingual pressure, blue line represents submental muscle activity. A- 50% of participant's MIP, B- line indicating start of trial, C- line indicating end of trial.

9.2.3 Experimental procedure

Calibration of the lingual bulb to atmospheric pressure occurred prior to the session, this was done as per the standard Kay Pentax operating instructions, using the internal calibration of the system. Prior to electrode placement, the skin was prepared with an alcohol wipe to remove oils from the skin surface to reduce impedance from the sEMG signal. The self-adhesive triode electrode patch was positioned over a participant's submental muscles with the two recording electrodes at midline and the ground electrode lateral. The patch was held in place with medical tape to aid adherence. The air-filled lingual bulb was placed on the

alveolar ridge, ensuring that all parts of the bulb were posterior to the central incisors so the participants could not use their teeth to produce pressure on the bulb. Participants were instructed to hold this in place using their hands, holding the connecting tubes just anterior to the lips. Participants were seated comfortably and it was ensured that they were able to view the monitor of the swallowing workstation.

To determine an individual's MIP, participants were asked to press their tongue against the bulb as hard as possible for three seconds, and the peak of the pressure produced was recorded. The researcher used the software to place a threshold line on the screen at 50% of a participant's MIP (line A, figure 9.1). In the lingual endurance task, participants were instructed to press their tongue against the bulb such that the pressure waveform remained just above the threshold line for as long as possible. As in previous research, if lingual pressure dropped below the 50% MIP line for two seconds or below 40% of MIP for more than 0.5 seconds the trial concluded (Kays, Hind, Gangnon, & Robbins, 2010; Vanderwegen, Guns, Van Nuffelen, Elen, & De Bodt, 2013). Participants were given a 15 sec break between trials, during which they were instructed not to talk or apply any pressure to the bulb. The researcher monitored this time on a stopwatch and after 12 seconds, participants were given a three second countdown and instructed to complete the task again. This task was repeated for a total of eight trials. During each trial, participants were given verbal encouragement to keep the waveform above the threshold line for as long as possible, as encouragement has been shown to increase performance (Andreacci et al., 2002). Although the sEMG waveform was not hidden, participants were oriented towards the lingual pressure waveform and were told to focus on keeping lingual pressure just above the line.

9.2.4 Outcome measures

Muscle activity for each trial was measured by sEMG in microvolts (μV) and lingual endurance time was measured in seconds (s). The Kay Pentax Digital Swallowing Workstation produces a rectified waveform and therefore true root mean square could not be calculated. To produce an average amplitude from the sEMG waveform, the area under the curve of the rectified sEMG waveform (μV s) was divided by the lingual press duration (s). Each trial was measured from the point in which the lingual pressure first crossed the line indicating 50% of MIP (see line A. figure 9.1). The trial concluded at the point when lingual pressure crossed the 50% MIP line before it dropped below 50% of MIP for 2 seconds or below 40% of MIP for 0.5 seconds (see line B in figure 9.1).

Inter-rater reliability of measurement was completed for 20% of trials selected by a random number generator. Inter-rater reliability was calculated for the time of a trial and for the area under the curve of the sEMG waveform. The second rater was a trained speech-language pathologist with no experience using lingual pressure or sEMG as outcome measures. Rules regarding when an attempt commenced and concluded were provided in written format and training of the second rater was completed through practice on data that were not selected for inter-rater reliability.

9.2.5 Statistical analyses

All statistical analyses were completed using RStudio software (version 1.2.5033) with R (version 3.6.2 for windows). Assumptions of normality and equality of variance were assessed. If the assumption of normality or equality of variance was not met, the non-parametric Friedman's tests were used to determine if there was an effect of multiple attempts. If a Friedman's test highlighted a significant change across attempts then Wilcoxon signed ranks tests were used post-hoc to assess the comparisons of interest. Comparisons were selected a priori. Each attempt was compared to the previous attempt to determine if there was gradual change in measures of fatigue and the first attempt compared to the final attempt to determine if there was an overall fatigue effect across sessions. Bonferroni corrections were used to correct for multiple comparisons. As there were eight comparisons made, the p-value indicating significance was adjusted to be 0.00625.

Inter-rater reliability was calculated using intra-class correlation coefficients (ICCs) derived from a linear mixed models analysis. A two-way random effects model based on single measures (ICC[2,1]) was used. Participant and rater were random effects in the model with only an intercept as a fixed effect. When assessing inter-rater reliability, each attempt at the task was considered independent.

9.3 Results

Inter-rater reliability was excellent for both task duration (ICC = 99.8 [95% CI = 99.7, 99.9]) and sEMG amplitude (ICC = 99.28 [95% CI = 98.7, 99.6]).

The data for duration of lingual endurance did not meet the assumptions of normality and equality of variance, therefore a Friedman's test was performed. There was a significant effect of gender (X^2 [1] = 4.5, p = .033) but not age group (X^2 [1] = 2, p = .157) on lingual

endurance time. Over all trials, females produced a median endurance time of 19.75 seconds and males produced a median endurance time of 15.46 seconds.

There was a significant effect of trial (X^2 [7] = 41.826, $p < .001$) on duration of lingual endurance. Median endurance time was 34.6 seconds for the initial attempt and 13.9 seconds for the final attempt. Post-hoc analysis showed that duration of lingual pressure was significantly shorter on the final attempt compared to the initial attempt (V = 255, $p < .001$). When comparing each attempt to the previous attempt, there was no significant change ($p > .006$).

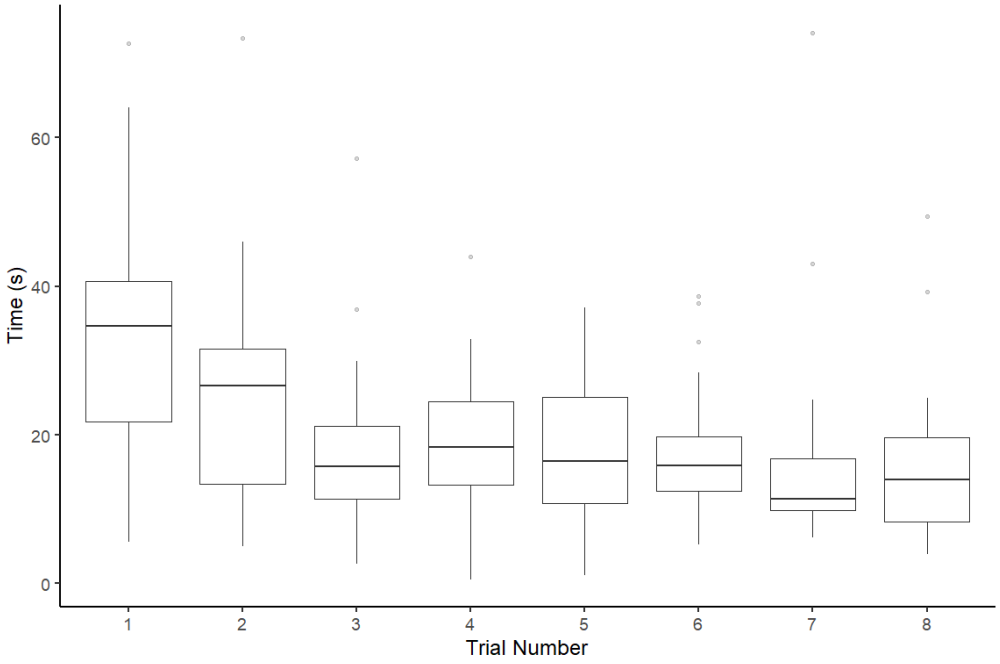

Figure 9.2. Boxplot of duration of lingual endurance over eight trials.

The average sEMG amplitude data did not meet the assumptions of normality and equality of variance; therefore, a Friedman's test was performed. There was a significant difference in average sEMG amplitude between trials (X^2 [7] = 14.30, p = .046). None of the pairwise comparisons were significant at the a priori determined level of significance following adjustment for multiple comparisons ($p < 0.006$; details in appendix). The difference between attempt seven and eight was approaching significance with attempt eight demonstrating a higher average sEMG amplitude than the seventh attempt ($p = .007$).

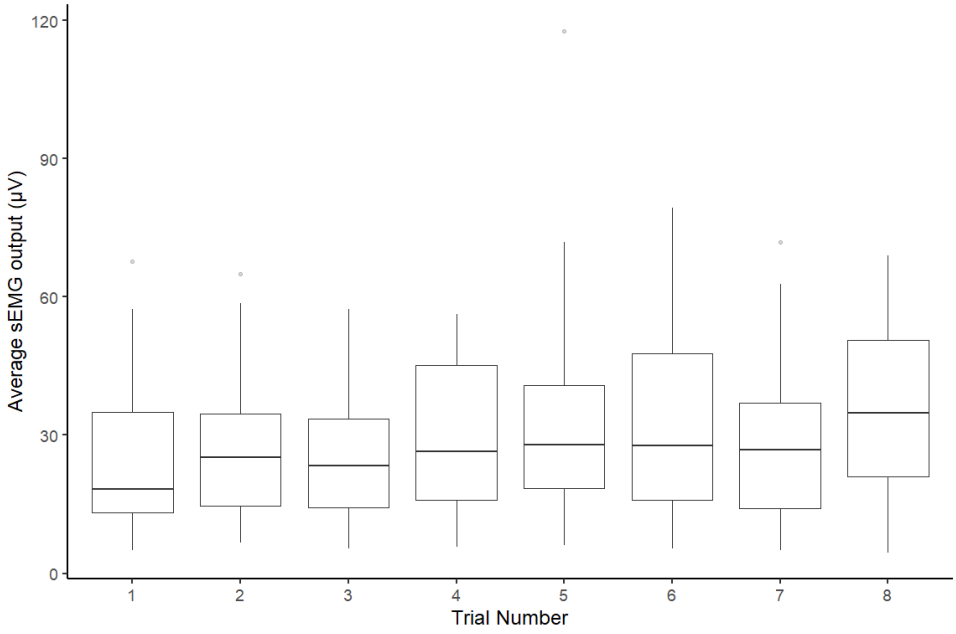

Figure 9.3. Boxplot of average activation of submental muscles over eight trials.

9.4 Discussion

The gold standard method for measuring muscle fatigue requires complex equipment and algorithms, which are not likely to be used in a clinical setting. This study represents an exploratory investigation into the use of a simple average sEMG amplitude to determine bulbar muscle fatigue. The methods used in the current study were not sufficient to document an increase in sEMG amplitude over trials, which would have indicated increasing fatigue. Therefore, further research is necessary to refine methods of measuring fatigue of submental muscles using non-invasive, clinically accessible means.

The results demonstrated a significant reduction in lingual endurance time between the first and final attempts; this likely indicates fatigue as a result of task repetition. A reduction in lingual endurance as a result of fatigue has been demonstrated in previous research (Kays et al., 2010). Kays et al. (2010) recruited 22 healthy participants and assessed lingual endurance at 50% of MIP both before and after a meal using the Iowa Oral Performance Instrument (IOPI). Both young and older participants demonstrated a reduction in anterior lingual press endurance time following the meal compared to the baseline condition. In the current research, significant changes in lingual endurance time were not observed between chronological attempts, which would have suggested a gradual onset of fatigue with task repetition.

Levels of patient motivation may have also contributed change in endurance time over trials. During the current study, participants received immediate visual biofeedback of their performance, as well as verbal encouragement, which has been shown to increase task performance (Andreacci et al., 2002). However, a limitation of all isometric endurance tasks is that factors such as a participant's motivation, tolerance to discomfort and competitive spirit can contribute to their performance (Solomon, 2004). If participants were to lose motivation by the later trials, despite no change in fatigue, this could have contributed to the significant findings for a reduction in time and lack of significant findings for increase in average sEMG amplitude.

There was no significant change in average sEMG amplitude between trials. This is contrary to the hypothesis that increasing levels of fatigue due to task repetition would result in an increase in sEMG amplitude. There are multiple possible explanations for this finding. The lack of significant change in average amplitude may be due to the fact that sEMG is not specific to a single muscle and the contribution of each muscle to the output is dependent on the proximity to the recording electrodes. Anterior tongue to palate pressure is produced by the genioglossus, mylohyoid, anterior bellies of the digastric, medial pterygoid and intrinsic tongue muscles (P. M. Palmer et al., 2008). The intrinsic tongue muscles, anterior portion of the geniohyoid and the submental muscles are all primarily made up of type II muscle fibres (Korfage, Schueler, Brugman, & Van Eijden, 2001; Saigusa, Niimi, Gotoh, Yamashita, & Kumada, 2001; Stål, Marklund, Thornell, De Paul, & Eriksson, 2003), which are designed for fast, frequent bursts of activity but not for endurance tasks. Therefore, these muscles fatigue quickly. With the electrode placement that was used, the submental muscles produce the majority of the electrical signal picked up by sEMG (P. M. Palmer et al., 1999). If other contributing muscles become fatigued prior to the submental muscles, it could result in the observed decrease in lingual endurance time without evidence of submental muscle fatigue identified by sEMG.

For many participants, the amplitude of the sEMG waveform appeared to increase within the trial as lingual pressure begins to drop (figure 9.1). It is possible that this indicates fatigue of submental muscles within a trial that was not observed between trials. Participants were given a 15 sec break following each trial, this may have allowed muscle recovery and have limited the findings of increasing sEMG amplitude between trials. Alternatively, this could indicate a pattern of muscle activation in which intrinsic lingual muscles are primarily recruited to

achieve tongue to palate approximation. However, as intrinsic lingual muscles begin to fatigue, extrinsic muscle activation occurs to compensate for fatiguing intrinsic lingual muscles to maintain tongue to palate pressure. Thus, the increase in sEMG amplitude observed within a trial may be the result of increased power output of the submental muscles rather than submental muscle fatigue.

Although it was not the purpose of the study, gender and age effects were investigated. There is debate in the literature regarding the presence of a gender effect on lingual endurance time. Studies in English and Portuguese speaking participants have found no differences between males and females in lingual endurance time at 50% MIP (Stierwalt & Youmans, 2007; Vitorino, 2010) and a study in Belgian participants demonstrated longer lingual endurance in males than females (Vanderwegen et al., 2013). In the current study, there was a significant difference in lingual endurance between genders with females producing a longer lingual endurance time than males. The current sample size was much smaller than that of previous studies and therefore may not be representative of the population. The finding that lingual endurance did not vary in response to age mirrors many previous studies that have also demonstrated no significant effect of age on lingual endurance time (Stierwalt & Youmans, 2007; Vanderwegen et al., 2013; Vitorino, 2010).

9.4.1 Limitations and future research

This study relied on the assumption that fatigue would increase over trials. Lingual endurance time decreased significantly between the first and last trials, with gradual decline over sequential trials. This may indicate fatigue over trials; however, this cannot be confirmed with the current research methods. Further research to develop a clinically friendly method of quantifying fatigue of bulbar muscles would be beneficial for patients with dysphagia. In future research it would be useful to simultaneously collect sEMG frequency data as this is the gold standard for non-invasive assessment of muscle fatigue, and would therefore help to determine if muscle fatigue is occurring and validate the average sEMG amplitude data.

It was observed in the current study that sEMG output increased within a trial; however, there was no change between trials. There was a 15 sec rest period between each of the trials, which may have been sufficient for some degree of recovery from fatigue. If participants had time to recover between trials, then it is unsurprising that there was no significant changes in fatigue levels measured by sEMG. Further research investigating changes within a trial or

without significant rest time between trials may be beneficial at determining the use of this method of detecting fatigue.

A further limitation of this study is that many muscles are recruited to produce tongue to palate pressure but sEMG in the position used during this study primarily provides information regarding activity of the submental muscles. If using surface electromyography in the position used in this study, it would be of benefit to assess submental muscle activity during a task in which the submental muscles are the primary muscles utilised.

10. Skill training for swallowing and quality of life in patients with MND

10.1 Introduction

Dysphagia is a symptom experienced by between 73% and 98% of patients with MND (A. Chen & Garrett, 2005; Kühnlein et al., 2008; Onesti et al., 2017). The cause of dysphagia in this population is likely a combination of both UMN and LMN degeneration leading to weakness of pharyngeal muscles as a result of spasticity and flaccidity. Any and all phases of swallowing can be affected over the course of MND. Oropharyngeal dysphagia can result in malnutrition and aspiration pneumonia, which can lead to death (Corcia et al., 2008; Yang et al., 2011). It is also one of the largest contributors to reduced quality of life in this population (Paris et al., 2013). Despite this, exercise to prevent or improve dysphagia is not often recommended (Plowman et al., 2017). This is likely due to a historical belief that exercise results in muscular fatigue leading to worse outcomes for patients. However, recent literature demonstrates that exercise at a mild to moderate intensity may have positive outcomes (Carreras et al., 2010; Plowman et al., 2019; Plowman, Watts, Tabor, et al., 2016).

A series of publications by Plowman and colleagues investigated the impact of expiratory muscle strength training (EMST) for patients with MND (Plowman, 2015; Plowman et al., 2019; Plowman, Watts, Tabor, et al., 2016). Following a training period, patients in the treatment groups demonstrated an increase in maximum expiratory pressure. However, despite the authors reporting significant results, differences in swallowing outcomes between the treatment and control groups were not as compelling. Although strengthening of submental muscles is a benefit of EMST, the task is not specific to swallowing. It is possible that the lack of specificity in conjunction with decreased task intensity contributed to the limited improvement observed in swallowing outcomes despite increase in maximum expiratory pressure.

Skill training for swallowing is a novel, swallowing specific treatment approach that has the potential to increase neuroplasticity and cortical excitability. To increase the likelihood of neuroplasticity, it is important to practice a task that is specific to the skill that it is intended to improve, with maximised intensity, repetition and long continuous bursts of training (Kitago & Krakauer, 2013; Robbins, Butler, et al., 2008). However, for patients with this rapidly neurodegenerative disease, the potential for skill training to induce neuroplasticity has

not been investigated. Importantly, there is evidence of early cortical reorganisation during swallowing in patients with a diagnosis of MND, but this is not associated with functional swallowing changes (Li et al., 2009). However, as the disease progresses and functional changes to swallowing become evident, a progressive reduction in cortical activation has been observed (Li et al., 2009; Teismann et al., 2009). These data suggest spontaneous neuroplasticity compensates for functional changes early in the disease, with disease progression presenting as both neural decline and progressive dysphagia.

SEMG has been used as a swallowing biofeedback modality for decades (Crary & Baldwin, 1997; Huckabee & Cannito, 1999). However, the investigation regarding its use for skill-based training is much more recent. A skill training protocol has been investigated in patients with Parkinson's Disease and was found to have significant beneficial effects on both functional swallowing outcomes and quality of life following two weeks of daily treatment (Athukorala et al., 2014). The authors hypothesised that these changes may be a result of greater voluntary control of swallowing, with increased cortical activation allowing patients to partially bypass the defective basal ganglia. As dysphagia is also progressive and neurological in origin for patients with MND, it is reasonable to hypothesise that a similar pattern of change will be observed in this patient group with MND.

This research programme consisted of a pilot and a treatment study. The pilot study aimed to determine if it was feasible to complete skill training using the BiSSkiT software in a population of patients with MND and to determine if it was feasible to recruit an adequate sample size for the study within Christchurch, NZ. Following completion of the pilot study, the treatment study was initiated with methods that were adapted in response to results of the pilot study. The aim of the treatment study was to investigate the effects of skill training for swallowing on swallowing outcomes and quality of life in a larger patient cohort. As this was early exploratory research, a large number of outcome measures investigating swallowing function, biomechanics and quality of life were probed in an attempt to determine which areas of swallowing may be improved through this skill training protocol.

10.2 Methods

10.2.1 Participants

The pilot study aimed to recruit ten patients with a diagnosis of MND within Christchurch in a one-year period. Participants were recruited through the support worker and specialist nurse

within the Motor Neurone Disease Association or the SLT. Participants received continued usual care from their SLT throughout the protocol; this did not, by report, include any active swallowing treatment. An explanation of the study protocol was given and written informed consent was obtained from all participants prior to participation. As methods were adapted for the treatment study, data from the initial five patients were not included in the final analysis. The initial participant in the pilot study was seen as a clinical patient at the Rose Centre for Stroke Recovery and Research and his results were included retrospectively. He therefore did not complete all of the assessments and some of his treatment sessions were conducted in his home without a researcher present. This study was approved by the University of Canterbury Human Ethics Committee.

The subsequent treatment study aimed to recruit 24 participants with complete data sets from Auckland (NZ), Christchurch (NZ) and New York City (USA). Patients aged 18 or over with a diagnosis of MND made by a neurologist, and no history of any other neurological, structural or muscular conditions that may influence swallowing outcomes were recruited through the NZ MND Registry, the National ALS Registry (USA), SLTs and the Canterbury MND nurse specialist. At the initial meeting, patients were assessed using the EAT-10 (Belafsky et al., 2008). A score greater than three, indicating self-perceived presence of dysphagia, was the final inclusion criteria. If a patient fit the inclusion criteria, demographic information was collected at the initial screening session. This demographic information consisted of MoCA and ALSFRS-R score as well as patient reported information about date of diagnosis, date of initial symptoms, medications and age. The treatment study was approved by the Health and Disability Ethics Committee for participants in NZ and the Teachers College, Columbia University Institutional Review Board for participants in New York City.

10.2.2 Study design

Given the degenerative nature of the disease and small population size, a within- subject treatment design was employed with an A-B-A approach to account for natural decline over a period of no treatment. Within the A-B-A approach, participants completed four assessment sessions with daily treatment sessions, five days per week, between assessments two and three and usual care alone between assessment one and two and between assessments three and four (figure 10.1).

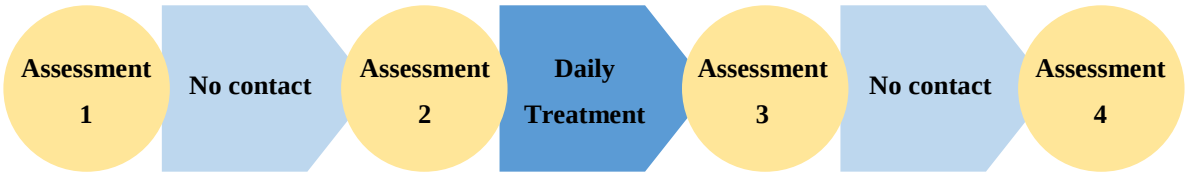

Figure 10.1. Study design.

At the time the pilot study was conducted, the plan for the treatment study was to compare skill training to strength training using expiratory muscle strength training (EMST). In the pilot study, assessments were four weeks apart with four weeks of daily treatment sessions between assessments two and four to align with a protocol for EMST. Time commitment was reported to be a limiting factor for participation in the pilot study and including the EMST protocol as a comparison condition was determined to not be feasible for the treatment study. Because of these factors, assessments were two weeks apart for the treatment study with two weeks of treatment between assessment two and three, effectively halving total participation time from twelve weeks to six weeks, and aligning participation time with a prior study of swallowing skill training using the BiSSKiT software in Parkinson's disease (Athukorala et al., 2014).

Data was collected by three researchers to facilitate this multi-site study. The primary researcher collected data at all three sites, with data collection completed by the secondary and tertiary researchers if the primary researcher was at an alternate site. The primary researcher completed training with the secondary and tertiary researchers, including joint assessment and treatment sessions to ensure that all researchers were completing the protocol in the same manner. Assessment and treatment sessions were completed with one of the researchers at either the Rose Centre for Stroke Recovery and Research (University of Canterbury) in Christchurch, North Shore Hospital in Auckland, or the Upper Airway Dysfunction Lab (Teacher's College Columbia University) in New York City. If a participant was unable to attend sessions at the centre in their region due to mobility issues or distance, treatment sessions were conducted in their home. All assessments in Christchurch and Auckland were completed at the University of Canterbury Rose Centre for Stroke Recovery and Research and North Shore Hospital respectively. Assessments in New York City, were completed either in the participants' homes or at the Upper Airway Dysfunction Lab at Teacher's College, Columbia University.

Materials:

10.2.2.1 Ultrasound

For the pilot study, a Siemens Acuson Antares™ ultrasound system (Siemens Medical Solutions, USA) was utilised, with a CH6-2 curved array transducer for hyoid excursion and a VF13-5 linear transducer to measure the CSA of the submental muscles.

For the treatment study, Clarius™ ultrasound scanners and software (Clarius, Burnaby CA) were utilised to allow for portability, accompanied by increased researcher training to facilitate optimal image quality. The Clarius™ linear scanner with a frequency range of 4-13 MHz and depth of 1-7 cm was used to collect images of the CSA of the submental muscles. The Clarius™ curvilinear scanner with a frequency range of 2-6 MHz and depth of 3-30 cm was used to collect images of hyoid excursion. Image depth and gain were set as per the pre-set exam type within the Clarius™ scanner; these were pre-determined to provide the best image quality. For hyoid images the 'Abdomen' setting was selected (depth of 7-10 cm, frequency of 4 MHz, single focus, dynamic range of 52dB). However, depth, gain and screen brightness were manually adjusted by the researcher to enhance the images. The scanners wirelessly connected with an iPad (Apple, CA) through Wi-Fi to allow visualisation and recording of videos and images within the Clarius™ app. Recordings were each 20 seconds long and saved at 20 frames per sec on a web-based cloud.

For all ultrasound data acquisition, aquasonic transmission gel was used to reduce reflection between the air and skin surface and enhance the image. Data acquisition was performed with a handheld transducer, without a stand to allow for optimal positioning and image quality (S. E. Perry, Winkelman, & Huckabee, 2016).

10.2.2.2 Videofluoroscopic swallowing study

At the Rose Centre for Stroke Recovery and Research, VFSS images were captured and recorded at 25 frames per seconds using an OEC FluoroStar 7900 series scanner (GE Healthcare,USA). At North Shore Hospital, VFSS images were captured and recorded at 30 frames per sec using a Toshiba Ultimax Fluoroscopy unit and a Medi-capture USB 170 recorder (USB 170 Medicap). Low dose continuous screening modes were used in both locations. Videofluoroscopy was not available for patients seen in New York City.

Liquid and puree boluses were prepared with a 40% w/v ratio of barium sulfate concentration using X-OPAQUE_HD Barim Sulfate Suspension formation (MCI (Aust) PTY LTD, Vic) mixed with water for liquid or Watties for Baby™ apple or apple and peach for pureed consistency. ARNOTT'S Salada™ original crackers were spread with a thin layer of E-Z-PASTE Barium sulfate oesophageal cream (60%w/w) (E-Z-EM Canada Inc., Canada) for the standard consistency.

10.2.2.3 Pharyngeal manometry

A ManoScan™ ESO Z catheter (Medtronic, Minneapolis) was used. It consisted of 36 circumferential pressure sensors and 18 impedance sensors spaced 1 cm apart and housed in a 4.2 mm diameter catheter. Each sensor consisted of 12 circumferential elements; the readings from each of these elements were averaged to derive the reading for a given sensor. This catheter was connected to a ManoScan 360™ (Model A120) (Medtronic, Minneapolis) system which uses the inbuilt ManoView™ software to display the data.

10.2.2.4 SEMG hardware and BiSSkiT software

Treatment sessions and skill assessments utilised single channel sEMG hardware (Neurotrac™ Simplex, Verity Medical Ltd., UK) and the Biofeedback in Strength and Skill Training (BiSSkiT) software (Huckabee, Sella, Jones & Han, 2016). Triode silver-silver chloride electrodes, with 2 cm spacing between electrodes and contained on an adhesive patch (Triode™ Electrode, Thought Technology Ltd., Canada) were connected to the sEMG device. Information was sent from the sEMG device to the software via fibreoptic cable plugged into the computer's USB port. A laptop computer was used when the treatment or assessment occurred at a participant's home, North Shore Hospital or the Upper Airway Dysfunction Lab and a desktop computer for the participants who completed treatment at the Rose Centre for Stroke Recovery and Research. The computer used for each participant was kept consistent across all treatment and assessment sessions. The sEMG data were displayed through the BiSSkiT software as a time by amplitude waveform, with time in seconds on the x-axis and amplitude of muscle activity in µV on the y-axis. The BiSSkiT software has options for strength and skill training protocols; the skill training protocol was utilised for this research.

10.2.2.5 Data extraction and analysis

A desktop computer with Quicktime™ player (version 7.7.9, 1680.95.84, Apple Inc.) was used to review Ultrasound, VFSS, TOMASS and TWST videos. Timing measures were extracted from Quicktime player using the movie inspector function. For all distance measurements, still images were extracted from Quicktime player and opened in ImageJ (version 1.50i, National Institutes of Health, Bethesda, MD) (Schneider, Rasband, & Eliceiri, 2012). GNU Image Manipulation Program (GIMP, version 2.10.14, Spencer Kimball, Peter Mattis and the GIMP Development Team) was used to align VFSS images for hyoid excursion, which were then measured using ImageJ. All statistical analyses were completed using RStudio software (version 1.2.5033) with R (version 3.6.2 for windows).

10.2.3 Experimental Procedure:

10.2.3.1 Pilot study assessment sessions

10.2.3.1.1 EAT-10 and Swallowing Quality of Life

In the pilot study, participants completed the EAT-10 and Swal-QOL questionnaires at the beginning of each assessment session. Participants would do this independently when possible; however, if assistance was required for physically completing the form, the researcher or a family member would provide assistance by reading the questions and circling the answer that the participant provided.

10.2.3.1.2 The Timed Water Swallowing Test and the Test of Masticating and Swallowing Solids

Following completion of the surveys the participants completed the TWST. Participants were instructed to drink 150 mL of water "as quickly as is comfortably possible" (Hughes & Wiles, 1996). If a participant was unable to complete the 150mL of water due to coughing or discomfort then the assessment was terminated and the amount of water that was left was recorded and calculation titrated to the ingested amount. If a participant was unable to hold a cup to their mouth and was comfortable using a straw, then a straw was used with the researcher holding the cup in place for the participant. The use of a straw was kept consistent across assessment sessions. The TOMASS was completed after the TWST as there is less likelihood of oral-pharyngeal residue from liquid than solid bolus ingestion, which might

have influenced the subsequent assessment. To complete the TOMASS, participants were instructed to eat one portion of an Arnott's SALADA™ cracker "as quickly as is comfortably possible" and say their name when they had finished (Huckabee et al., 2017). If a participant nibbled small amounts of cracker rather than biting, they were stopped and instructed to begin again without nibbling.

Clinical judgement was used to determine if it was unsafe for a participant to proceed with these assessments; amount of coughing, number of swallows and participant discomfort were taken into account. Both the TOMASS and TWST were video recorded with an Apple iPad. The iPad was held by the researcher to view the participant in a lateral view and allow for optimal visualisation of movement of the thyroid cartilage when swallowing. The eyes were not included in video recordings to increase participant confidentiality. Following completion of the TOMASS, participants were offered a sip of water to clear any sensation of pharyngeal residue before proceeding.

10.2.3.1.3 Speech assessments

Vowel prolongation, alternating motion (/pa/, /ta/, /ka/) and sequential motion rate (/pataka/) tasks were completed by participants. For vowel prolongation, participants were instructed to sustain /ah/ for as long as possible three times with a one-minute break between trials to avoid fatigue. For alternating and sequential motion rates, participants were instructed to repeat the given sound as quickly and clearly as possible for five seconds. Each sound (/pa/, /ta/, /ka/ and /pataka/) was repeated three times. All speech assessments were recorded on a voice recorder.

10.2.3.1.4 Ultrasound

For collection of ultrasound data, participants sat comfortably in a chair or their own wheelchair with their head in a neutral position and their back against the back of the chair. Ample gel was applied to the transducer for coupling. Imaging of hyoid excursion was completed first. For these measures the transducer was placed in the midsagittal plane, as seen in Figure 10.4. This allowed for visualisation of the acoustic shadows produced by the hyoid and mandible bones. Minimal pressure was applied to avoid depression of soft tissue, which results in distorted images (Stone, 2005).

Participants performed three dry swallows, three 5 mL puree swallows from a spoon and three 5 mL thin water swallows from a 20 mL medicine cup in sequential order. The 5 mL bolus size was selected for puree and water swallows as patients with neurological disorders resulting in dysphagia are often unable to consume large boluses in one swallow (Ertekin, Aydoğdu, & Yüceyar, 1996). Participants were instructed to hold the bolus in their mouth until the transducer was positioned to achieve a clear image, then the instruction was given to swallow when they were ready. For consistency, the image was orientated with the skin surface at the top, lingual surface at the bottom, the mandible on the left side of the screen and the hyoid on the right. If a participant coughed, swallowed multiple times or continued to move following the initial swallow, this would be noted and the transducer held in place to obtain a rest image once the participant's muscles relaxed. If the participant was unable to stop moving (e.g. severe coughing) so that a rest image could not be obtained within the 20 sec video limit the trial was repeated after the movement subsided.

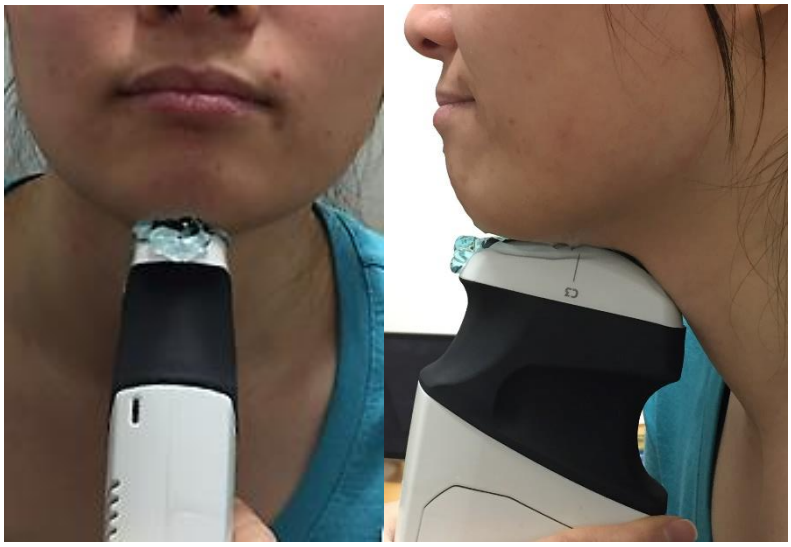

Figure 10.4. Clarius^{TM} handheld transducer placed in the midsaggital plane to measure hyoid excursion.

Following the acquisition of data for hyoid excursion, videos of the CSA of the submental muscles were collected. Participants were instructed to sit as still as possible with their lower back against the back of the chair and without hyperextending their neck. The Clarius linear transducer was placed on the coronal plane under the chin (Figure 10.5) with minimal pressure applied to ensure the images were not distorted. The pre-selected setting for submental muscle CSA was the 'Breast' setting on the Clarius^{TM} scanner (depth of 3-5 cm, frequency 10 MHz, dual focus, dynamic range of 65dB). Depth, gain and screen brightness

were manually adjusted by the researcher as necessary to ensure optimal image quality. A 20 sec video was acquired as the transducer was slowly moved anteriorly to posteriorly over the muscles (left anterior belly of the digastric, right anterior belly of the digastric and GH^{+}). To ensure that there was an image that could be accurately measured, each muscle was imaged separately. Videos of the CSA of submental muscles were acquired without a bolus.

Figure 10.5 Clarius^{TM} handheld transducer placed in the coronal plane to measure cross sectional area of submental muscles.

10.2.3.2 Treatment study assessment sessions

Treatment study assessment sessions began with filling in the Swal-QOL survey, followed by the TWST, the TOMASS and US using the same methods as described for the pilot study with one adaptation. During Ultrasound, measurements were made by the researcher between boluses using the software within the Clarius^{TM} app on the iPad. This gave participants approximately one minute of rest between each swallow. As they were not blinded, these measurements were not included in the final analysis; this process was completed to ensure adequate quality of videos for later analysis. Details of the measurements made are in the data extraction section (section 7.2.5.4). If a video and the reviewed images were deemed not of adequate quality measurement, the bolus trial was repeated and measured. Following these assessments, further instrumental analyses were completed as outlined below.

10.2.3.2.1 Swallowing skill

In assessment sessions three and four, following ultrasound data acquisition, a measure of swallowing skill was collected. This information was then compared to the first ten swallows of the initial treatment session to determine change in swallowing-skill over time. Participants completed ten swallows using the skill training aspect of the BiSSKiT software on the same computer that was used for a patient's treatment sessions. The sEMG electrodes were attached and calibrated as per treatment sessions. Ten saliva swallows were performed using the skill training aspect of the BiSSkiT software with the instruction to aim for the centre of the target box. Visual feedback of success was displayed on the screen as in the treatment sessions. If a participant was unable, or did not attempt, to initiate a swallow on a trial, the trial would be repeated on the following screen.

10.2.3.2.2 Videofluoroscopic swallowing study

VFSSs were completed by two trained researchers or SLTs; an additional radiographer assisted with all VFSSs at North Shore Hospital. A radiopaque coin of either 18 mm or 20 mm (dependent on VFSS location) was adhered under the participant's chin that was used for image calibration. Participants sat in either their own wheelchair or a chair with a back and arm rests for comfort.

Prior to video recording, still images were taken to ensure the correct positioning. It was ensured that the nasal cavity and velopharyngeal port, anterior aspect of the mandible, the cervical spine and the superior portion of the oesophagus could be visualised. Once positioning was confirmed, a bolus hold video was acquired to obtain an image of structural position at rest. To acquire the hold position participants held a 1 cc puree bolus (no barium) in the oral cavity and were instructed not to swallow, this was recorded for approximately two seconds. Participants then performed three non-cued swallows of 5 cc boluses of thin liquid mixed with barium followed by three 5 cc boluses of puree mixed with barium. Boluses were measured with a syringe; liquid boluses were given to the participant in a 20 mL medicine cup and puree boluses on a spoon. If the participant was not able to independently bring the cup or spoon to their mouth, the researcher would assist with feeding. Screening began when the spoon or cup reached the participants lips and continued until structures returned to an approximate rest position following the initial swallow. At the Rose Centre for Stroke Recovery and Research the researcher was able to start and stop screening

independently; at North Shore Hospital, the researcher indicated to the radiographer when to start and stop screening. Following the puree boluses, the participant completed three swallows, each of a bite of SALADA cracker lightly coated with barium paste. Bite size and mastication time were determined by the participant. To minimise radiation exposure during mastication, participants were instructed to chew the bite of cracker for as long as they needed and to indicate to the researcher just before they were ready to swallow by raising a finger or nodding, dependent on the participant's range of movement. The researcher or radiographer would then begin screening and the researcher would instruct the participant to swallow when they were ready. If the participant had pharyngeal residue following a bolus they were instructed to perform dry swallows or ingest sips of water taken from a cup until the residue was cleared.

10.2.3.2.3 Pharyngeal manometry

In the treatment study, participants in Christchurch underwent high resolution impedance manometry (HRIM). HRIM was not used at North Shore Hospital or the Upper Airway Dysfunction Lab due to resource limitations. Routine in-vivo calibration as well as standard calibration were performed prior to use, using the calibration protocol within the ManoScan system according to the manufacturer recommendations. The participant was seated in a comfortable chair or wheelchair with a high back to prevent the participant leaning away from the researcher during catheter insertion. To determine which nasal passage was more open the participant was asked to cover one nare and inhale and then to repeat with the other nare covered. The nasal passage deemed to be more open was used for catheter placement. Topical nasal anaesthetic was not used as in healthy participants it has been found to not reduce discomfort but it may alter swallowing pressures (Guiu Hernandez et al., 2018; Kwong, 2018). A lubricating gel was applied to the end of the catheter to facilitate insertion (Omari et al., 2019). The catheter was placed through the selected nare and inserted using a standard procedure (Knigge, Thibeault, & McCulloch, 2014; Omari et al., 2019). Once the catheter reached the pharynx, as indicated by resistance at the pharyngeal wall, participants were instructed to look up so the catheter could be manoeuvred around the nasopharyngeal angle. Participants were then instructed to return their head to a neutral position and swallow sips of water at their own pace as the catheter was passed through the pharynx and into the proximal oesophagus. Once the catheter was inserted with the final sensor just inside the nare

and the lower sensors in the oesophagus, the catheter was taped securely to the participant's nose to ensure that it remained in place throughout the assessment.

Prior to bolus ingestion, participants were given five minutes to become accustomed to the catheter in situ (Omari et al., 2019). Participants then performed three dry swallows followed by three 5 mL swallows of saline from a 20 mL medicine cup and three 5 mL puree boluses (apple sauce mixed with saline) from a spoon. A bolus size of 5 mL was selected as it is consistent with other instrumental assessments in this study and it is the most commonly used bolus size for pharyngeal manometry (Omari et al., 2019). Three swallows of a consistency is considered the minimum number that is sufficient for internal consistency when using pharyngeal manometry (Omari et al., 2019). Each swallowing event was marked on the Manoscan system by the researcher.

If at any point the participant experienced extreme discomfort (e.g. continued gag reflex) as a result of catheter placement, the study was terminated. If the participant could not tolerate catheter placement on the first assessment it was not repeated at subsequent assessments.

10.2.3.3 Treatment sessions

10.2.3.3.1 Calibration

The computer and sEMG device were placed on a table within reach of the participant and researcher. Participants were seated in a comfortable chair or their wheelchair and encouraged to wear any corrective lenses necessary to ensure that they could view the computer screen. The area of skin over the submental muscles was prepared using an alcohol wipe. The electrode patch was adhered with the active electrodes placed over the submental muscles and the ground electrode placed laterally (figure 10.2), over the mandible. The wires were placed over the ears to reduce the chance of movement artefact and to prevent the electrode patch from being pulled off due to the weight of the wires. When necessary, the patch and electrodes were secured with medical tape to aid adherence. A sEMG reading at rest with noise less than 10μV was ensured prior to starting a session. This was achieved by turning off nearby electrical appliances that might have interfered and ensuring adequate connection between the sEMG electrodes and the skin's surface. If turning off nearby appliances was not possible and noise could not be reduced when in a participant's home, a new electrode patch with repeated skin preparation and/or a different area of the home were trialled until noise was reduced to the required level.

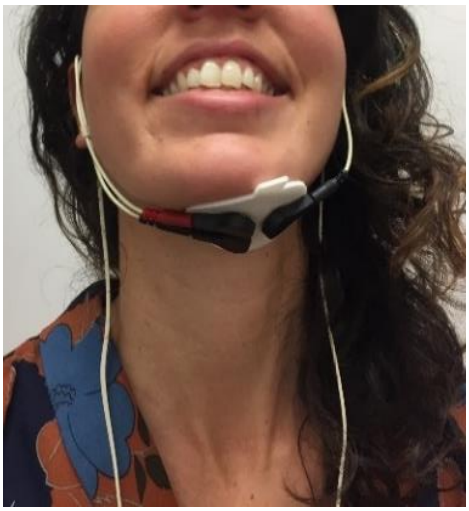

Figure 10.2. Placement of surface electromyography (sEMG) electrode patch.

Once the noise was under 10 µV with the patient sitting at rest, the device was zeroed to ensure that the waveform represented only movement-related activity. To zero the device, the participant was instructed to sit as still as possible and not swallow for 10 seconds. The waveform was monitored by the researcher to ensure that no swallows or extraneous movement occurred. After 10 seconds, the "Remove DC offset" button on the BiSSkiT software was pressed and the waveform dropped to zero. Calibration was completed at the start of every session. To calibrate the device, participants were instructed to swallow their saliva "as hard as possible". If this instruction was not sufficient, the researcher would tell the participant to "swallow hard as if you are swallowing a golf ball". The researcher observed laryngeal movement of the patient to ensure that a peak in the waveform represented an observed swallow. When a swallow was identified, the researcher marked the peak of the waveform representing the swallow by placing a cursor with a right mouse click. Each screen sweep lasted 30 seconds, one effortful swallow was completed at any time on each 30 sec screen with rest between each swallow. If a participant was unable to elicit an effortful swallow within a screen sweep, they would be instructed to perform an effortful swallow in the following screen and this swallow would be marked; this was repeated until five swallows had been marked. The software then calculated the average value from the five calibration trials and this was set this as the maximum amplitude of the y-axis during the treatment task.

The calibration method was adapted following the pilot study as in this study it was observed that some participants were unable to produce swallows with peaks within the calibrated

screen range. For the treatment study, if the participant was unable to perform effortful swallows during calibration, the maximum value on the y-axis was adjusted to be 140% of the average of the five swallows from the calibration task. A participant was deemed unable to perform effortful swallows if their peak swallowing amplitude when performing a normal swallow was consistently greater than or equal to that of the effortful calibration swallows.

10.2.3.3.2 Treatment

Following calibration, the treatment task began. During the skill training task, the BiSSkiT software provided visual feedback represented by a time by amplitude waveform associated with activation of proximal muscles (figure 10.3). Due to the electrodes' position, a peak was observed in the waveform as the submental muscles contracted during swallowing. Increased swallowing effort resulted in increased muscle activity, and, in turn, a higher peak on the sEMG waveform (De Luca, 1997; Huckabee et al., 2005). The software produced a green target box randomly placed on the screen between 30% and 70% of the calibrated y-axis amplitude (i.e. between 30-70% of an individual's effortful swallow amplitude). Participants were instructed to swallow their saliva such that the peak fell as close as possible to the centre of the target box. This required precision in timing and relative degree of muscle activation during swallowing. The researcher observed the participant to ensure that swallowing had occurred and provided verbal feedback to the participant if waveforms were the result of submental muscle activation that was not associated with swallowing. When swallowing was identified, the researcher marked the event by right clicking on the peak of the waveform. Each screen sweep lasted 30 seconds with one target box per screen; this gave participants time between swallowing to generate saliva and prepare for the following attempt. If the participant swallowed multiple times on a screen the swallow that was closest to the target box was selected.

For each trial, success was defined by the peak of the waveform representing a swallow falling within the target box. Participants received immediate visual feedback to inform them of the accuracy of their performance. Following a swallow, a numerical figure representing the distance of the peak of the swallow from the centre of the target box and the word "hit" or "miss" would show, in green or red, respectively, depending on a participant's success (figure 10.3). The size of the target box was programmed to adapt dependent on success. The target decreased in size by 10% following three consecutive successful attempts; this made the task more challenging. Conversely, following three consecutive misses, the size of the target

increased by 10% to reduce task difficulty. The researcher provided verbal encouragement to ensure continued motivation to achieve success, and if a participant appeared to lose concentration during the task, the researcher would focus the participant, for example by asking “are you ready for the next swallow?” or stating “three more until the break”.

Participants completed 10 swallows per block, and eight blocks per session for a total of 80 swallows per session. The decision to use 80 swallows per session was made to limit the treatment sessions to one hour and reduce the risk of fatigue compared to 100 swallows per session used in previous skill training research (Athukorala et al., 2014). Each block of ten trials was separated by a 100-sec rest period during which the participant would be offered sips of water and given the chance to speak to the researcher. Conversation and drinking water was discouraged between swallows during the treatment task.

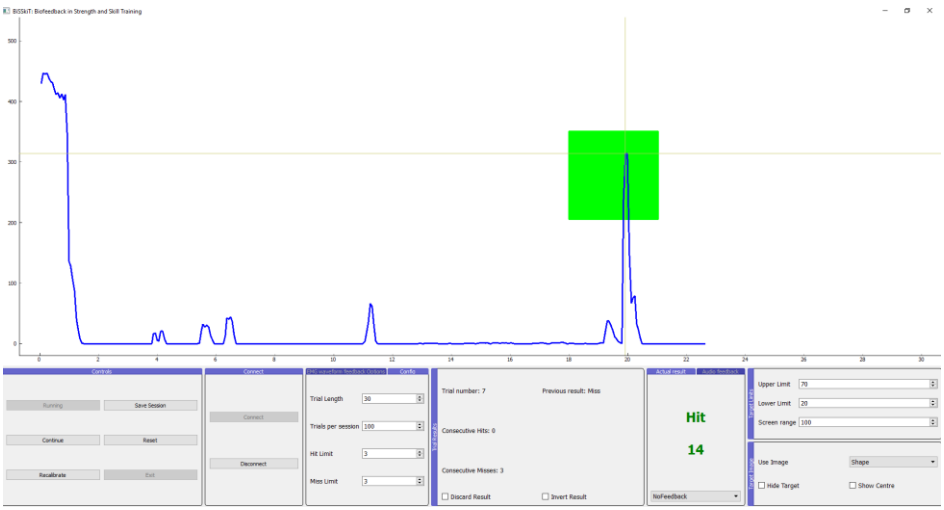

Figure 10.3 screen that a participant views during treatment. The blue line represents muscle activity and the green box is the target. The blue peak within the target represents the submental muscle activation during swallowing.

10.2.4 Data extraction

During the pilot study, all data were extracted online, and therefore, no blinding was in place. When analysing data for the treatment study, the researcher was blinded to session number for all analyses and additionally blinded to participant for ultrasound measures. Blinding to participant was not possible for TOMASS, TWST or VFSS analysis due to identifying features on the recordings.

10.2.4.1 Swal-QOL

Symptom frequency scores from the Swal-QOL survey were analysed. These included the total symptom frequency score (all 14 items from section three) and subscores for oral, pharyngeal and salivary symptoms. The oral symptom frequency subscore was calculated from three factors (drooling, problems chewing and food/liquid dribbling from the mouth), pharyngeal symptom frequency from seven factors (coughing, choking on food, choking on liquids, gagging, clearing throat, food sticking in throat and coughing when food stuck) and salivary symptom frequency from two factors (thick saliva and excess saliva) (McHorney et al., 2002). This produced an overall score for each of these factors out of 100.

10.2.4.2 TOMASS and TWST

Videos were extracted from the iPad onto a desktop computer. Each video was watched as many times as necessary to ensure analysis was as accurate as possible. The number of bites, masticatory cycles, swallows and time (in sec) were tallied for the TOMASS (Huckabee et al., 2017). The number of bites was determined by the number of discrete segments of cracker that the participant placed in their mouth. The number of masticatory cycles was counted by observing jaw movement. One masticatory cycle consisted of jaw opening and closing. Time started when the cracker passed the bottom lip and stopped when the participant said their name. Swallows were counted through observation of the movement of the thyroid cartilage. For the TOMASS, the raw data of number of bites, swallows, masticatory cycles and the time taken for a participant to consume a cracker were extracted from the video recordings.

The number of swallows and time taken were measured for the TWST. The number of swallows was counted through observation of movement of the thyroid cartilage. Time started when the cup was put to the lips and stopped when the thyroid cartilage returned to the rest position following the final swallow (Hughes & Wiles, 1996). Volume per swallow (mL consumed/number of swallows), time per swallow (number of swallows/ time taken) and volume per sec (amount consumed/time taken) were calculated in an excel spreadsheet.

10.2.4.3 Ultrasound

Videos were downloaded from the Clarius™ cloud onto a desktop computer. Quicktime™ was used to scroll through videos of hyoid excursion frame by frame to select the frame in

which the hyoid was at rest and the frame in which it was at maximum excursion. The rest frame was always a frame following the swallow. The frame for maximum hyoid excursion was that in which the shadow of the hyoid was deemed to be most approximated to the shadow cast by the mandible. If piecemeal swallowing occurred, the first swallow would be measured and the rest frame taken following the final swallow.

Measurements were made in a dark room using the straight line function in the image J software 1.50i developed by the National Institutes of Health (Schneider et al., 2012). The measurements were calibrated using reference points on the right of the image (figure 10.6), each of which were one centimetre apart. A best-fit reference line was placed along the anterior edge of the acoustic shadow cast by the hyoid bone, which extended past the end of the shadow, towards the skin surface. This was done to help facilitate identification of the hyoid measurement point (figure 10.6, line D). The shadow cast by the mandible was used as a reference point from which to measure hyoid excursion (figure 10.6, point A) (Macrae et al., 2012). A line was drawn from the point on the shadow of the mandible at the posterior border where there was a sharp change in direction from vertical to horizontal to the point in which the line of best fit intersected the onset of the shadow cast by the hyoid bone (figure 10.6, line E). The length of this line was measured in mm. This measurement was done first in the rest image to calculate H_{rest}, followed by H_{max} using the maximally approximated image. The researcher was able to play or scroll through the video at any point in making measurements to track movement. Hyoid excursion was calculated as a percentage change of the total distance between the hyoid and mandible at rest $\frac{\text{Hrest} - \text{Hmax}}{\text{Hmax}}$.

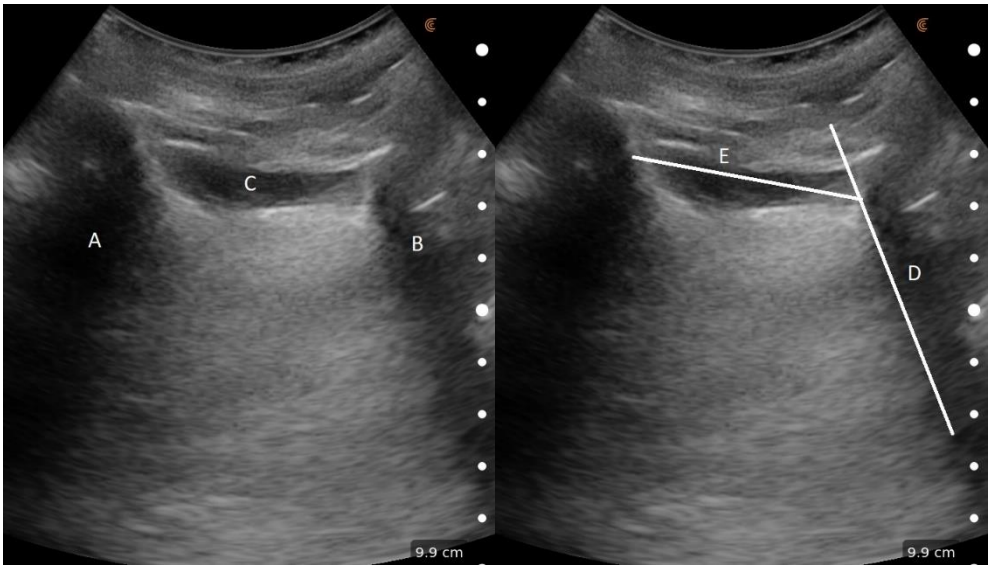

Figure 10.6. A – acoustic shadow from the mandible, B – acoustic shadow from the hyoid bone, C- GH^+ muscles, D- guideline at the anterior portion of hyoid shadow, E – distance measured between hyoid and mandible.

For CSA of the submental muscles, the image selected was that in which the muscle was at its largest, yet still had clear borders. This was done by scrolling frame by frame through videos. The frame with the best image was selected for each muscle independently. The freehand measurement tool on the ImageJ software was used to outline the muscle borders. CSA of submental muscles were measured in mm^2. The left (figure 10.7, A) and right (figure 10.7, B) anterior belly of the digastric muscles were measured separately by tracing around the outer borders. The paired right and left geniohyoid muscles and part of the mylohyoid muscle (figure 10.7, C) were measured as one entity due to the inability to clearly and consistently identify boundaries between the muscles. This was consequently referred to as GH^+. This measurement ran along the inferior border of the mylohyoid muscle with a vertical line drawn to the point where the mylohyoid met the lateral border of the geniohyoid on both sides; this line followed down the lateral borders and across the superior border of the geniohyoid (bottom of image).

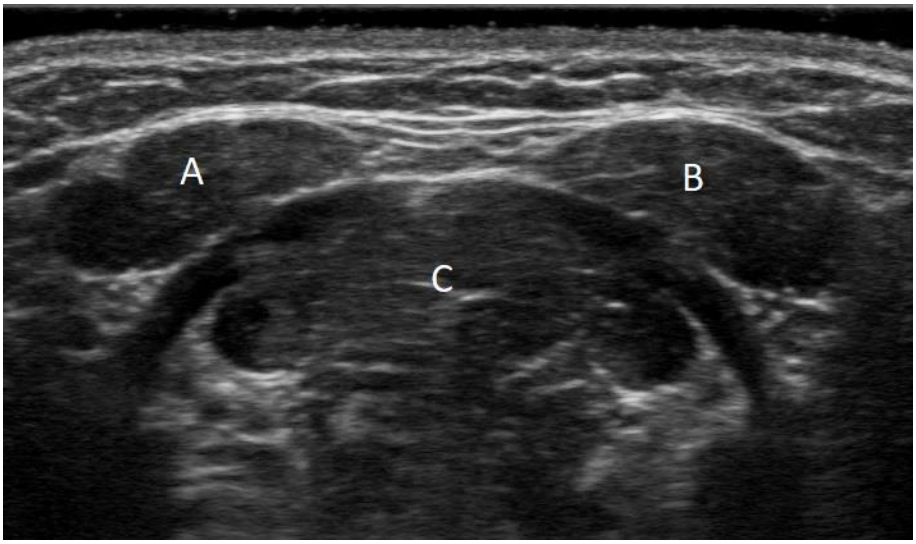

Figure 10.7. Ultrasound image of CSA of submental muscles, A- left anterior belly of the digastric muscles, B-right anterior belly of the digastric muscles, C- GH+ muscles.

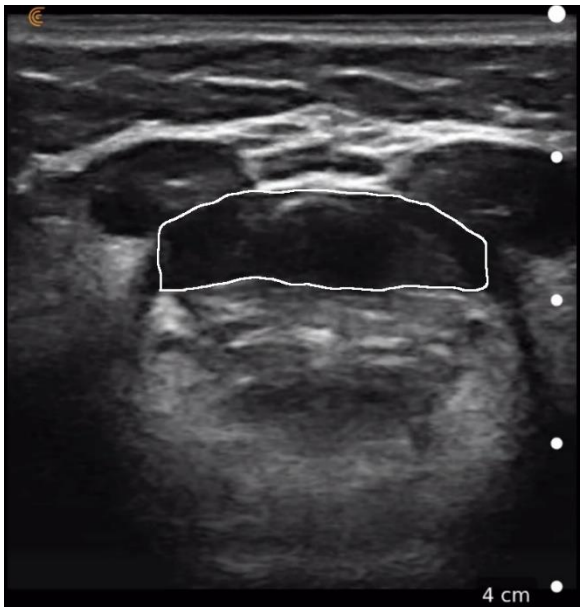

Figure 10.8. Measure of GH^{+} muscle complex

10.2.4.4 Swallowing skill

Session statistics were extracted from the BiSSkiT software into an excel spreadsheet. Data indicating amplitude and temporal error from the first 10 swallows of the initial treatment session and the same data from the first 10 swallows during the third and fourth assessment sessions were extracted.

10.2.4.5 VFSS

Timing measures of oropharyngeal physiology calculated from the fluoroscopic recordings included: oropharyngeal, hypopharyngeal and total pharyngeal transit time, timing of supraglottic closure, duration of airway closure and UES opening duration. Spatial measures were upper oesophageal sphincter opening, pharyngeal constriction ratio and hyoid displacement (Leonard & Kendall, 2008). Additionally, the Penetration-aspiration Scale (PAS) was used to quantify depth of and reaction to airway invasion (Rosenbek, et. al. 1996). Objective measurements of swallowing from VFSS followed instructions set out in the Dynamic Swallow Study (DSS) guidelines (Leonard & Kendall, 2018). VFSS videos were saved on a password protected USB and transferred to a desktop computer. For all measures image contrast and brightness were adjusted to enhance the image for optimal viewing as determined by the researcher.

The movie inspector function was used on Quicktime player to extract the time in the video that each of the following events occurred. B1 was the time in which the bolus passed the anterior portion of the nasal spine. BV1 was the time in which the head of the bolus reached the base of the valleculae. BV2 was the point in which the head of the bolus left the valleculae. BP1 was the time in which the head of the bolus entered the UES. BP2 was the time in which the tail of the bolus passed through the UES. AEstart was the time of the first superior movement of the arytenoid cartilage for airway protection. AEclose was the time in which the airway was fully closed. EM was the moment in which the epiglottis returned to its pre-swallow, upright position.

Formulas were established in Microsoft Excel and the following timing measures were calculated

- Oropharyngeal transit time (OPTT): BV2 -B1
- Hypopharyngeal transit time (HPTT): BP2 - BV2
- Total pharyngeal transit time (TPTT): BP2 - B1
- Timing of supraglottic closure: BP1 - AEClose
- Duration of airway closure: EM - AEClose
- Duration of UES opening: BP2 - BP1

VFSS spatial measures also followed the DSS guidelines by Leonard and Kendal (2018), with some minor variations due to the chosen software. The bolus hold frame was selected from the 1 cc puree bolus hold video as the frame in which the participant appeared most at rest. To measure maximum hyoid displacement, the frame in which the hyoid was maximally displaced both anteriorly and superiorly was selected. The hold and maximum displacement images were aligned to allow visualisation of the hyoid bone at rest and during the bolus hold within one image (figure 10.9). To align these images, first the hold image was opened and a straight line drawn from the anterior inferior portion of the C2 vertebrae to the anterior inferior portion of the C4 vertebrae. Additionally, the anterior inferior border of the hyoid bone was traced with a freehand drawing tool. The maximum hyoid displacement image was then opened as a layer and the same lines drawn from C2 to C4 and around the hyoid. Opacity of the overlaid image was set to 50% so that the hold image could be viewed through the superimposed image. The two images were aligned by moving and adjusting the angle of the maximal excursion image and using the line between C2 and C4 as a guide. Once aligned, images were saved as a jpg file. The overlaid image was opened in ImageJ and calibration was completed using the known dimensions of the coin placed under the chin. Measurement was made between the anterior inferior portion of the hyoid at rest and at maximum excursion in mm using the straight line measurement tool.

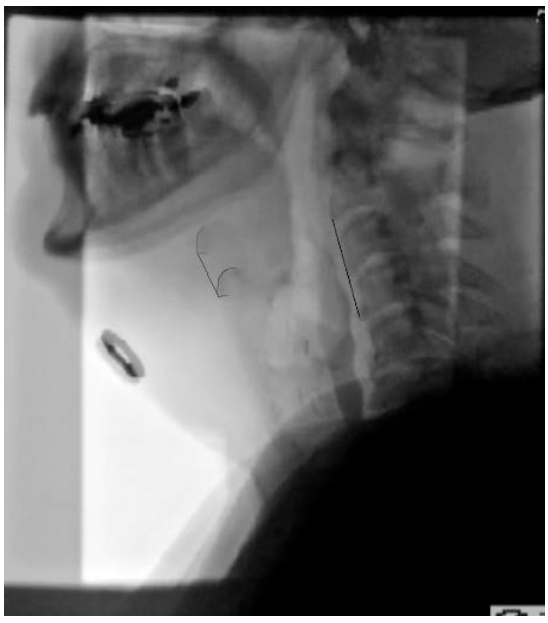

Figure 10.9. Rest and hyoid at max excursion images overlaid with measurement

The frame of maximal UES opening was selected by scrolling though the video to find the frame in which the UES was maximally distended. Calibration occurred prior to measurement using the known dimensions of the coin placed under a patients chin. The UES was selected as the narrowest point between C4 and C6 that was not the result of an osteophyte. Once the UES was located, the line drawing tool was used to measure in a straight line anterior to posterior across the shortest distance of the UES (figure 10.10).

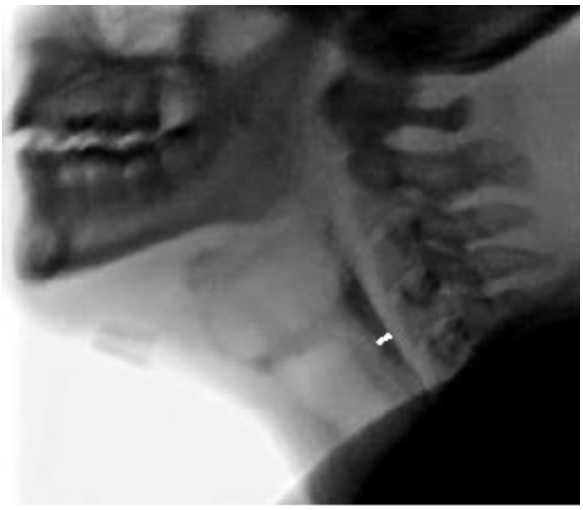

Figure 10.10. UES opening indicated by white line

To calculate pharyngeal constriction ratio (PCR) the pharyngeal area at rest (PA_{rest}) was compared to the Pharyngeal area when maximally constricted (PA_{max}). The same hold image was used as the hyoid excursion rest frame. The frame used to measure PA_{max} was found by scrolling through frame by frame on the on Quicktime player. The frame in which the pharynx was maximally constricted was selected. Frames were selected on a desktop computer then transferred to a Surface laptop (Microsoft®, NM, USA). Calibration occurred prior to measurement, by drawing a straight line anterior to posterior on the coin under the chin and setting dimensions to the known measurement. An electronic Surface pen (Microsft®, NM, USA) was used to outline the structures with the freehand drawing tool on the ImageJ software. To measure PA_{rest}, an outline was drawn that started at the posterior nasal spine with a straight line to the tubercle of the atlas, the line followed down the posterior pharyngeal wall and outlined the pyriform sinuses. The outline then traced around the anterior superior portion of the arytenoid cartilages and straight across to the epiglottis at the point of the connection of the thyroepiglottic ligament. It then followed the epiglottis, into the vallecular space, around the base of tongue and the soft palate. If the soft palate was not

visible then the line would connect straight up to, but not anterior of, the posterior nasal spine (figure 10.11). This area was measured in mm^2. PA_{max} was also measured using the freehand drawing tool and electronic pen. The area of bolus and any air that was visible in the pharynx at maximum constriction, but that was not connected to the body of the bolus, and not below the UES, was outlined and the area measured in mm^2 (figure 10.12). A ratio of maximum constriction to rest position was calculated by $\frac{\text{PAmax}}{\text{PArest}}$.

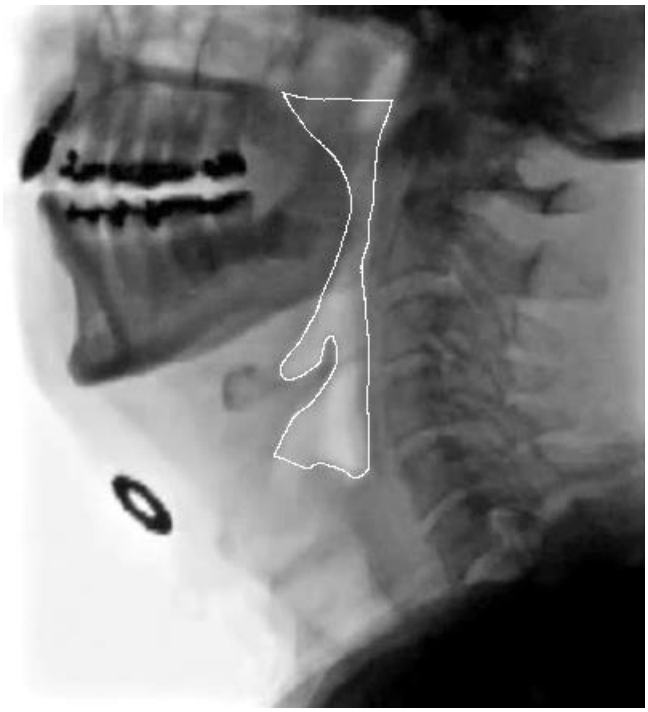

Figure 10.11. Measurement of PA_{rest}

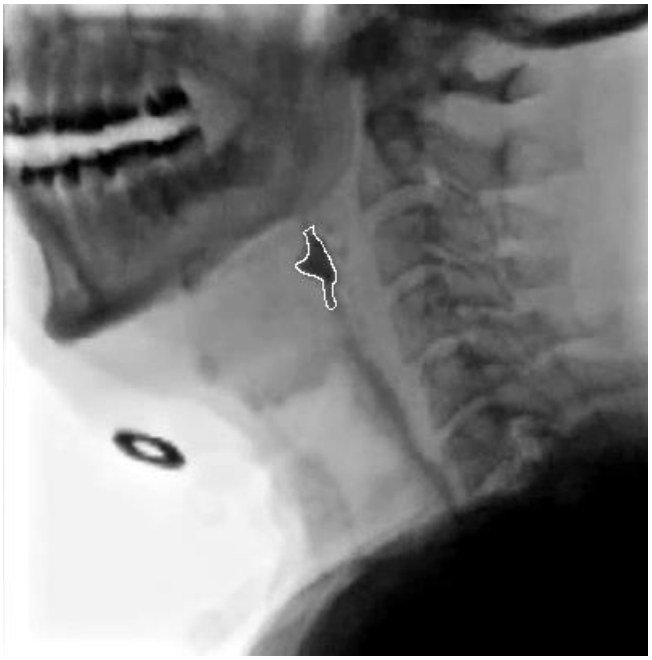

Figure 10.12. Measurement of PA_{max}.

10.2.4.6 Pharyngeal manometry

De-identified studies were taken from the ManoScan using a USB and uploaded to the Swallow Gateway™ webpage. Studies were saved without identifying material, only the randomly generated number produced during blinding. Swallow Gateway™ was used for analysis of pharyngeal impedance manometry, following the instructions in the user manual (Omari, 2020). To complete this semi-automated data-extraction, the researcher identified six landmarks through the software. These are the point of UES relaxation, time of UES contraction, position of velopharynx upper margin, position of hypopharynx upper margin, position of UES apogee and the position of the UES distal margin (Omari, 2020). If piecemeal swallowing occurred, the swallow with the largest bolus volume was analysed as per the Swallow Gateway™ instruction manual (Omari, 2020). Data were then exported from the software to an excel spreadsheet using the "EXPORT DATA" function. Data for Whole Pharyngeal Contractile Integral (PhCI) (mmHg.cm.s), Hypopharyngeal Contractile Integral (HPCI) (mmHg.cm.s), UES Integrated Relaxation Pressure (UESIRP) (mmHg), UES Relaxation Time (UES Open Time) (s), Hypopharyngeal Peak Pressure (PeakP) (mmHg), Hypopharyngeal Bolus Presence Time (BPT) (s) and Velopharyngeal to Tongue Base Integral (VTI) (mmHg.cm.s) were extracted.

10.2.4.7 Inter- and intra-rater reliability

Inter-rater and intra-rater reliability were completed on 20% of sessions which were randomly selected via a random number generator. Consensus-based training was completed with the primary researcher and secondary rater using data that were not selected for inter-rater analysis. This training followed a guide that was used by both the primary and secondary rater to follow when completing the ratings. Inter-rater reliability was performed by two separate researchers, one completed inter-rater reliability of ultrasound measures and the other of VFSS, TOMASS and TWST measures. Both raters had extensive experience in the areas that they were assigned. Two weeks following initial data extraction, the primary researcher re-rated the selected sessions for intra-rater reliability.

10.2.5 Statistical analysis

Analyses were completed in a stepwise fashion. First, data were assessed for normality and equality of variances to determine if parametric tests could be used for analysis. For the data which met the assumptions of normality and equality of variance likelihood ratio tests were used to determine if there was an effect of session. To do this, the full model, which included session as a fixed effect, was compared to the reduced model which did not contain session. If there was a significant session effect, further analyses were completed using the full model to further evaluate the changes across specific sessions. If the session effect was not significant at the 0.1 level then it was concluded that there was no significant difference between sessions, and therefore, the treatment had no statistically significant effect. A p-value of 0.1 level was selected a priori to ensure that post-hoc comparisons were completed to identify all potential significant differences between sessions. Comparisons were selected a priori and the differences between sessions 1 and 2, sessions 2 and 3 and sessions 3 and 4 were investigated. These sessions were selected as the difference between sessions one and two indicated natural change with no intervention, between sessions two and three indicated an effect of the treatment and between three and four investigated the maintenance effect after treatment. An alpha level of 0.05 was selected to indicate significance in pairwise comparisons. No adjustments were made for multiple comparisons. The study has a small sample size and therefore limited power, which inherently results in a large risk of a type II error (Christley, 2010; A. Smith, 2018). As this is exploratory research, decreasing the chance of type I error and therefore further increasing the chance of type II error through adjustments would be detrimental as it could result in overlooking potential clinical benefits (Althouse,

2016; Perneger, 1998). Linear mixed effects models were used with session as the fixed effect and participant a random effect for all assessments. If multiple boluses were used e.g. in VFSS and US measures then each bolus type was analysed independently.

If assumptions were not met, non-parametric tests were used. Again, these were done in a stepwise fashion, starting with Friedmans tests to determine if there was a difference between sessions. For boluses with multiple trials (e.g. VFSS and Ultrasound) the scores were averaged over these trials. If the p-value was significant at the 0.1 level, post-hoc analyses were completed using Wilcoxon signed ranked tests for the pairwise comparisons with the same comparisons as made in parametric testing. As with the parametric tests no adjustments were made for multiple comparisons and a p-value of .05 was accepted as a significant difference between sessions.

Additionally, the degree of change between periods was compared to determine if the treatment hastened or slowed the rate of decline in swallowing ability for a patient. To do this, three new variables were created: change over the treatment period (assessment 3-assessment 2) change over the baseline period (assessment 2 – assessment 1) and change over the maintenance period (assessment 4 - assessment3). As with the previous analysis, assumptions were assessed. Comparisons for post-hoc analyses were selected a priori with comparisons made between the baseline period and treatment period to determine if the treatment alters the usual rate of decline for a patient and comparison between the baseline and maintenance periods to determine if the rate of change returns to that of natural decline following the offset of treatment. If assumptions were met, linear mixed effects models were used to assess for an effect of period with follow-up pairwise comparisons to compare the aforementioned periods. This was done in the same manner as the previous analyses with the full model, which included period as a fixed effect, compared to the reduced model which did not include period. If there was a significant effect of period determined at the 0.1 level of significance, post-hoc analyses were completed using the full model to evaluate the changes between baseline and treatment and baseline and maintenance periods. If the effect of period was not significant at the 0.1 level then it was concluded that there was no significant difference between periods. If assumptions were not met, non-parametric tests were completed. Friedman's tests were used to determine if there was a significant difference between periods. Again, if there was no significant effect then no further analyses occurred. If there was a significant effect at the 0.1 level, post-hoc Wilcoxon signed rank tests were

used to complete pairwise comparisons of the aforementioned periods. The PAS is a categorical scale (Steele & Grace-Martin, 2017), therefore, descriptive statistics based on graphs of the raw data were used to describe the observed changes.

Inter-rater and intra-rater reliability were calculated for all outcome measures using intraclass correlation coefficients (ICCs) derived from linear mixed effects model analyses. For assessments with multiple swallows, each swallow was considered independent. For inter-rater reliability, a two-way random effects model based on single measures (ICC(2,1)) was used. Participant and rater were entered into the model as random effects, with bolus as a fixed effect if there were multiple consistencies trialled. If multiple boluses were not trialled (e.g. Swal-QOL and TOMASS) an intercept was the only fixed effect. Likelihood ratio tests were used to determine if there was a significant rater effect. For intra-rater reliability ICC(3,1) was used, derived from linear mixed effects model analyses. Bolus (when there were multiple consistencies trialled) and rating number were fixed effects with the measurement number as the random intercept. All models were tested for normality and equality of variance. An ICC value less than 0.5 was considered poor, between 0.5 and 0.75 was considered moderate, between 0.75 and 0.9 was considered good and above 0.9 was considered excellent agreement (Koo & Li, 2016).

As the PAS was considered a categorical variable, kappa statistics were used to calculate inter-rater and intra-rater reliability. The kappa statistic was calculated using the formula: $K = \frac{\Pr(a)-\Pr(e)}{\Pr(e)}$ where Pr(a) is the observed agreement and Pr(e) is the agreement expected by chance (McHugh, 2012). A Kappa of 0 - .2 was considered no agreement, .21 - .39 minimal agreement, .4 - .59 was considered weak agreement, .6 -.79 moderate agreement, .8 - .9 represents strong agreement and above .9 was considered almost perfect agreement (McHugh, 2012). Additionally, the absolute agreement for PAS was calculated by dividing the number of trials in which the two raters gave the same rating for the swallow by the total number trials.

10.3 Results

10.3.1 Pilot study descriptive results

10.3.1.1 Participants

Five participants were recruited for the pilot study. Three had a diagnosis of bulbar onset MND and two had a diagnosis of spinal onset MND. The average age was 59.8 with a range of 46 to 73. Gender ratio (M : F) was 4 : 1. All patients had an EAT-10 score > 3 (mean = 17, range = 4 to 28) at the time of the initial assessment, indicating abnormal swallowing (Belafsky et al., 2008; Plowman, Tabor, et al., 2016). Pt4 had a PEG tube in situ to supplement hydration but oral intake was his primary source of nutrition at the time of the initial assessment. Pt5 had a PEG tube inserted prior to the fourth assessment. Due to dysarthria, alternative communication using an iPad was Pt4's main source of communication; all others used verbal communication. No participants dropped out and all participants were able to participate in the treatment protocol despite concomitant limb, respiratory and speech symptoms.

Pt1 completed the final three weeks of sessions at home with once-weekly face-to-face check-in session to ensure correct procedure. The number of swallows completed per session by Pt1 ranged from 17 to 80, with an average of 67 swallows per session. Additionally, the participant reported that he would often complete the task sitting in front of the television.

10.3.1.2 Outcome measures

The data from TOMASS are detailed below in figures 8.13 - 8.16. For the three participants with mild to moderate dysphagia (Pt1, Pt2, Pt3), time taken to complete the TOMASS did not vary over the first three assessments (figure 10.13). However, following four weeks of no treatment, TOMASS time increased for two of these participants (Pt2 and Pt3) (Figure 10.13). Number of bites also appeared to be stable or decrease over the treatment period for all participants (Figure 10.14). Number of swallows increased over the treatment period for all participants (Figure 10.15). There was no pattern of change across participants observed for number of masticatory cycles (Figure 10.16). Pt4 was unable to complete the TOMASS in the first assessment due to a gagging episode that he could not control; however, he was able to complete the TOMASS in subsequent assessments. Pt5 had a PEG tube placed prior to assessment four and declined to complete the TOMASS.

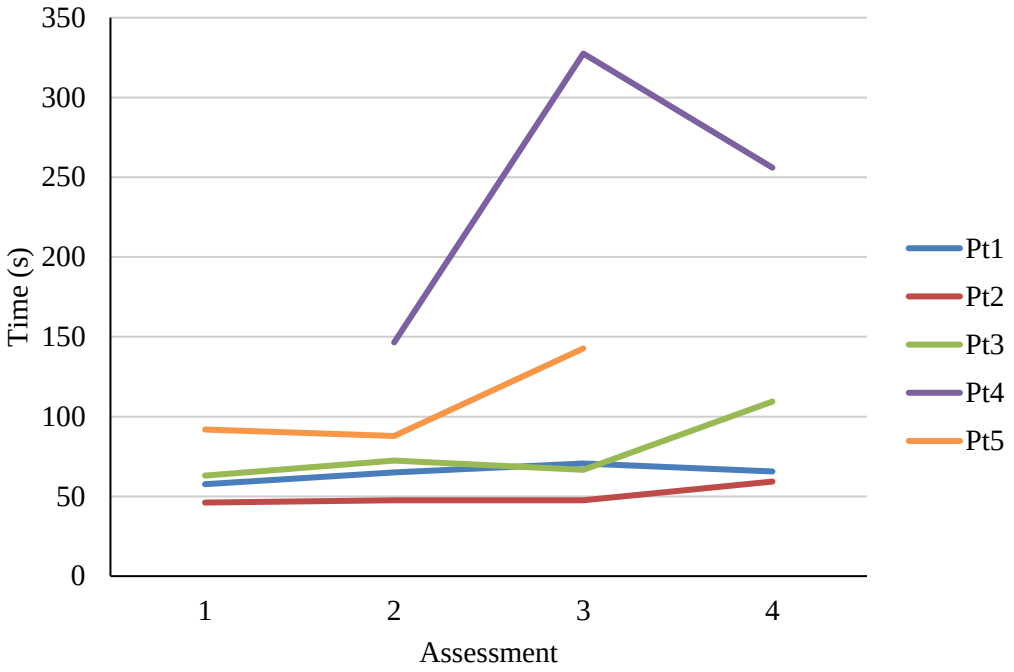

Figure 10.13. Time taken for patients to complete the TOMASS at the four assessment points.

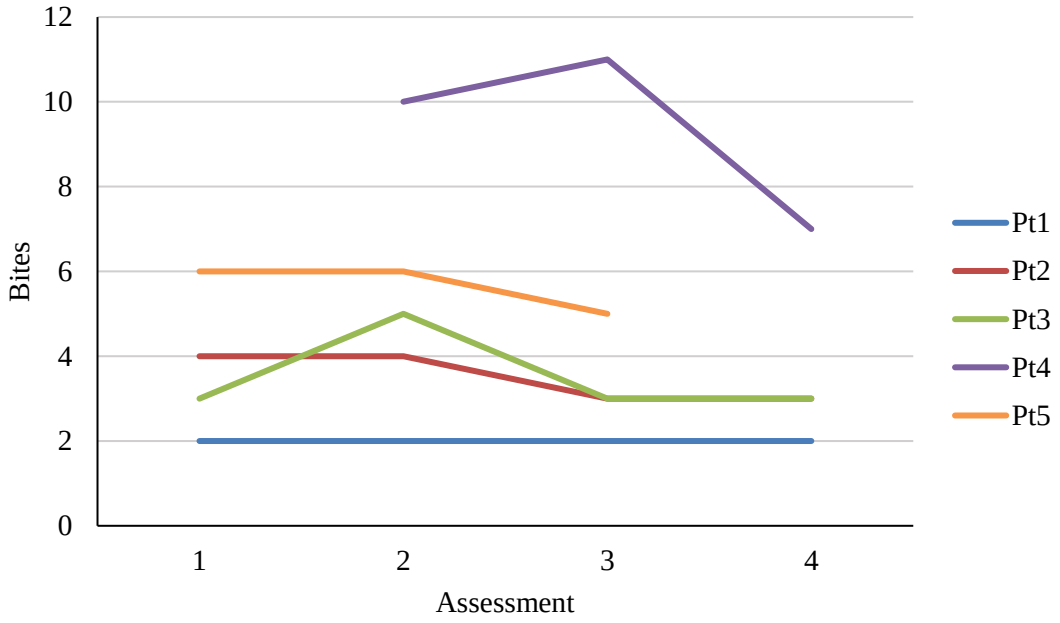

Figure 10.14. Number of bites taken for patients to complete the TOMASS at the four assessment points.

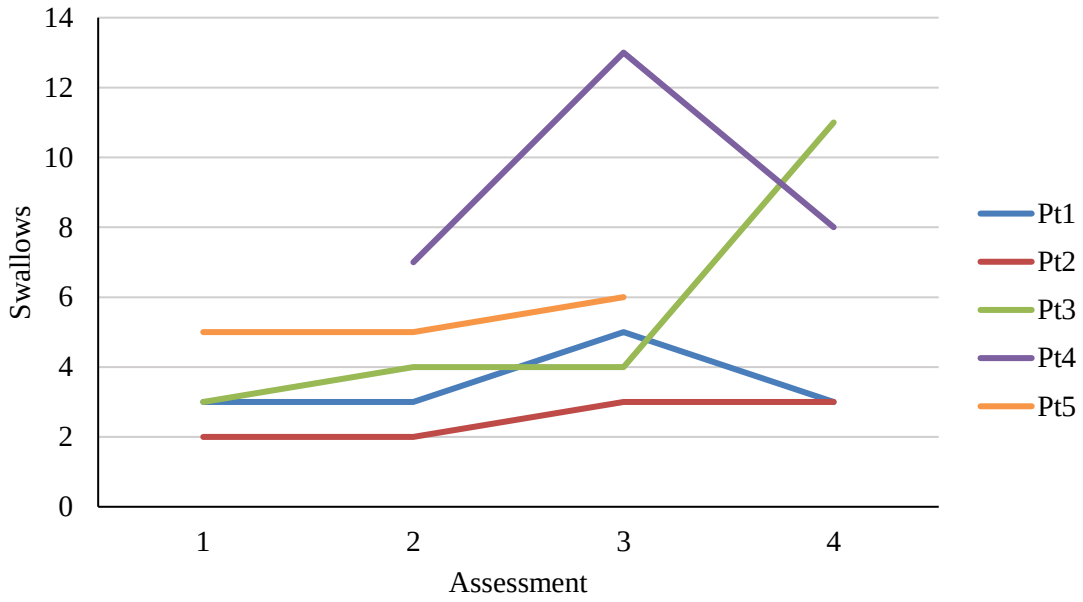

Figure 10.15. Number of swallows for patients to complete the TOMASS at the four assessment points.

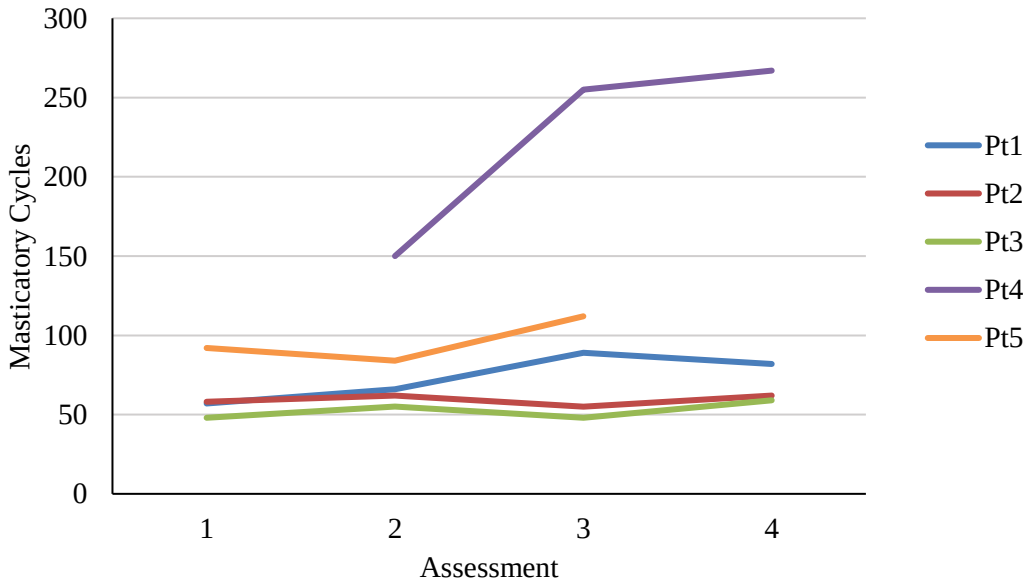

Figure 10.16 Number of masticatory cycles taken for patients to complete the TOMASS at the four assessment points.

Outcomes on liquid bolus ingestion measured by the TWST are displayed below in Figures 8.17-8.19. Swallowing capacity (figure 10.17), volume per swallow (figure 10.18) and time

per swallow (figure 10.19) increased or remained stable following treatment for the participants who were able to complete the test (Pt1, Pt2 and Pt3). This differed from the pattern seen over the baseline and follow-up periods of no treatment, during which decline in function was observed. Pt4 did not complete the TWST in any assessment due to drinking only thickened liquids with supplemental liquids that were delivered through his PEG tube. Pt5 was placed on thickened fluids prior to the post-treatment assessment and it was deemed unsafe for him to complete the TWST with thin liquids in the final two assessments.

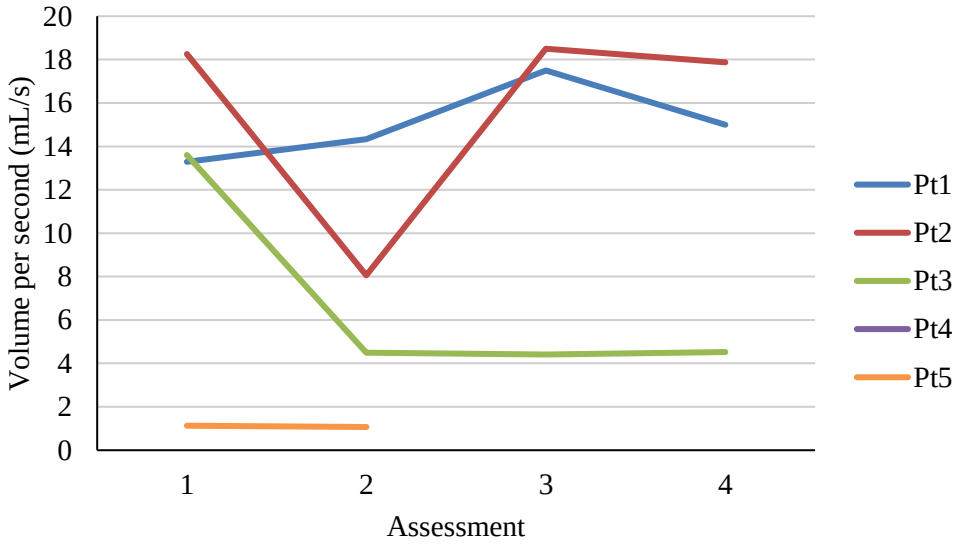

Figure 10.17. Volume of water consumed per sec when completing the TWST over the four assessment sessions.

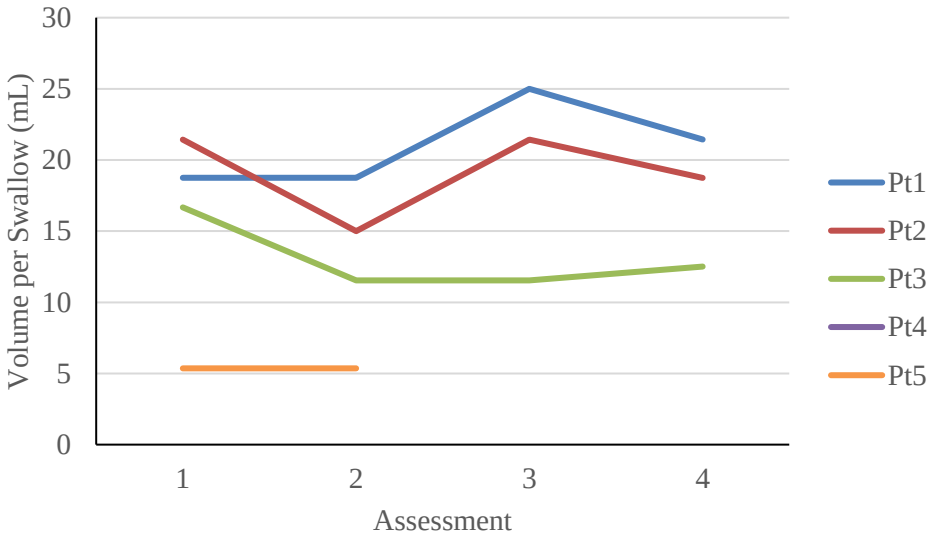

Figure 10.18. Swallowing efficiency, volume of water consumed in each swallow when completing the TWST over the four assessment sessions.

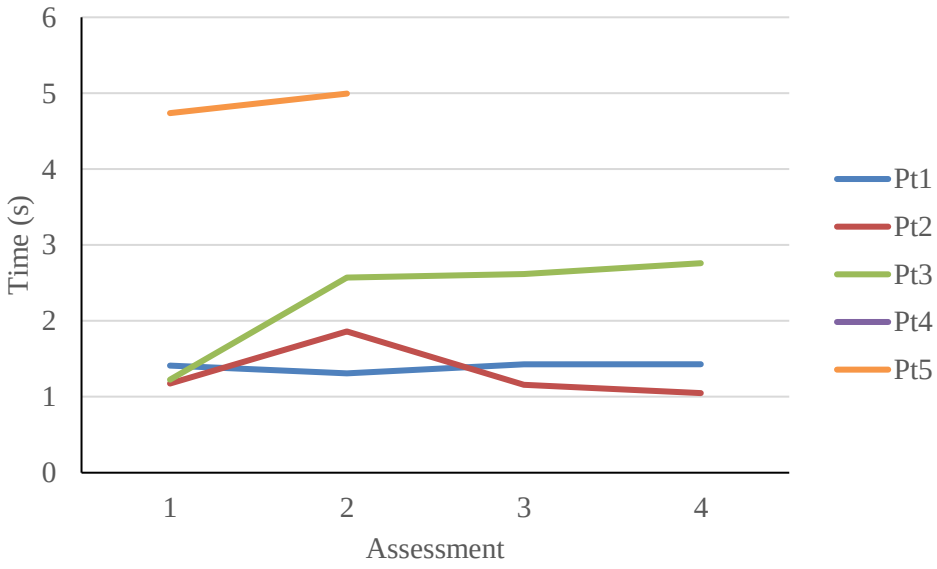

Figure 10.19. Time taken per swallow when completing the TWST in the four assessment sessions.

Participant's self-perception of dysphagia appeared to progressively decline for the participants with moderate-severe dysphagia (Pt4 and Pt5). Pt2 reported improved dysphagia over the treatment period and stabilisation over the follow-up period and Pt3 demonstrated

the opposite with a reduction in score over the treatment period and improvement in the baseline and follow-up periods (Figure 10.20). Pt1 did not complete the Swal-QOL as this was not included in assessments at the time of his participation.

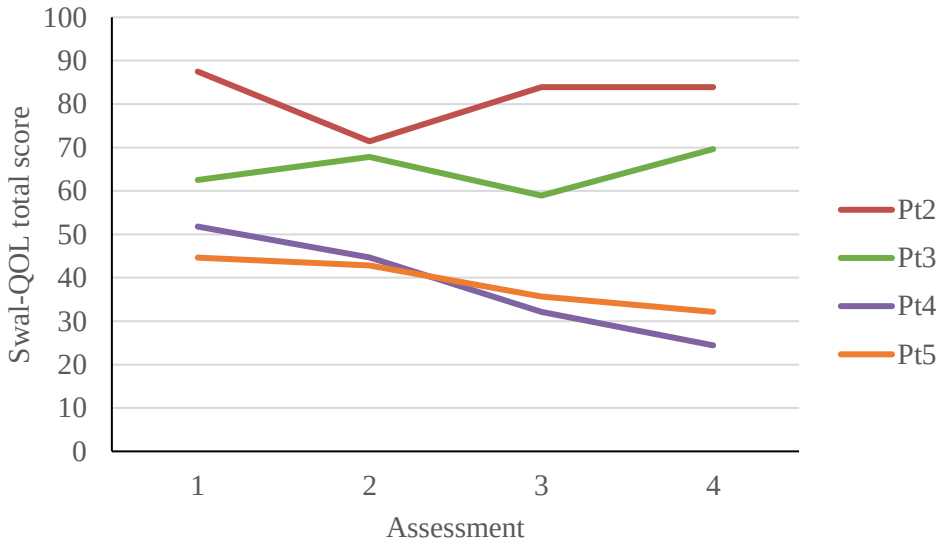

Figure 10.20. Total symptom frequency of participants over the four assessment sessions.

There was no consistent pattern of change in the EAT-10 over the assessments (figure 10.21). Of the two participants deemed to have severe dysphagia, Pt5 demonstrated improvement over assessments and Pt4 demonstrated decline. Pt2 and Pt3 demonstrated opposite patterns of improvement and decline over sessions (figure 10.21). Pt1 did not complete the EAT10 as it was not included in assessments at the time of his enrolment.

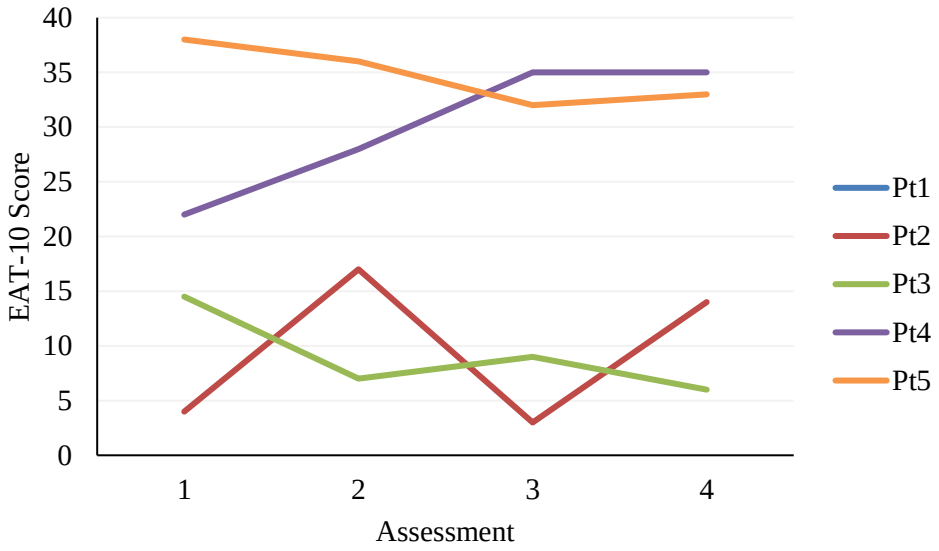

Figure 10.21. Self-reported dysphagia symptoms using the EAT-10 survey over the four assessment sessions.

The three participants who completed their assessment sessions in Christchurch underwent ultrasound. The ultrasound instrumentation used during the pilot study was not portable and therefore, was not able to be used with Auckland participants. The US images obtained were deemed to be of insufficient quality for reliable analysis. Therefore, there were no ultrasound data extracted for the pilot study.

Decline in measures of speech production appeared steady across all assessment points. Vowel prolongation declined for all participants except Pt2 who demonstrated a steady increase in length of prolonged “ah” (figure 10.22). Alternating and sequential motion rate appeared to decline steadily over the course of the assessments for all participants, this pattern of change was similar with all sounds produced (figure 10.23). Pt1 did not complete vowel prolongation or alternating motion rates as these were not included in assessment protocols as the time of his participation.

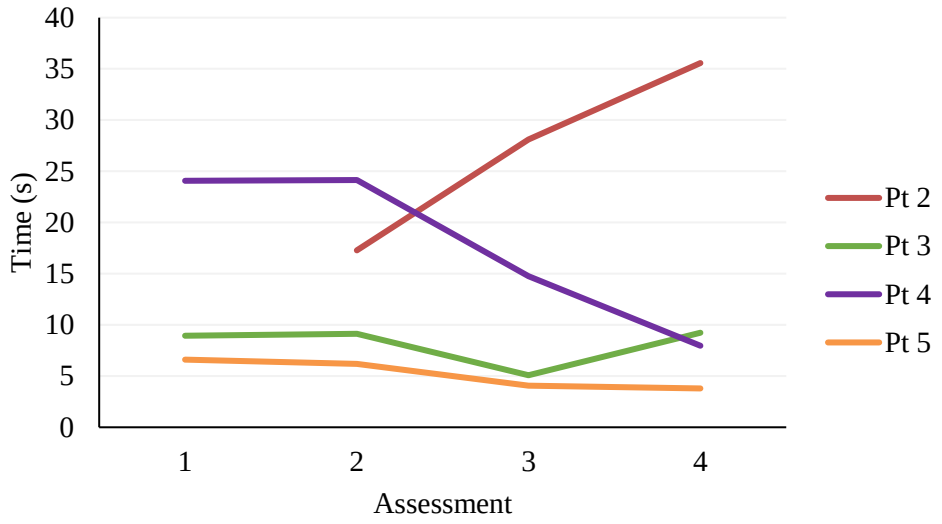

Figure 10.22. Vowel prolongation time over the four assessment sessions

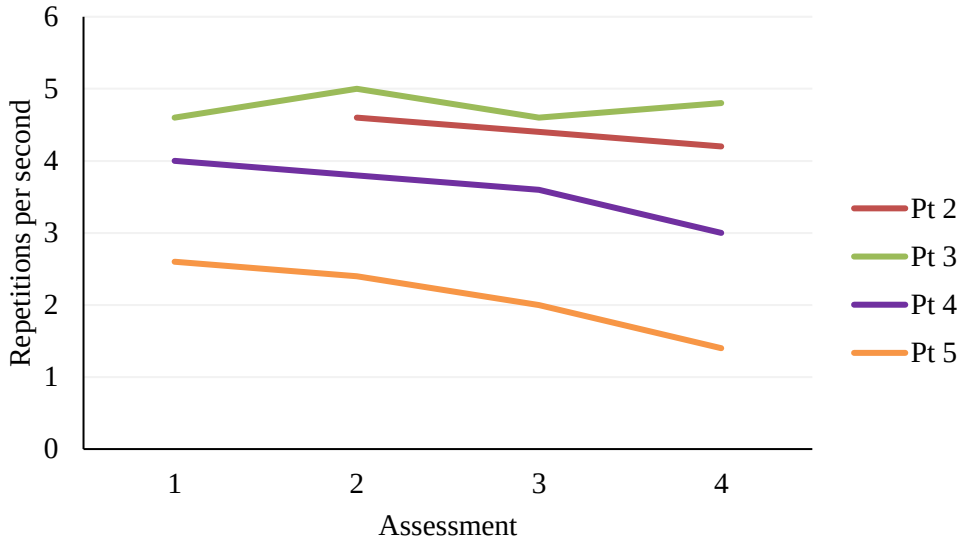

Figure 10.23. Alternating motion rate for "pa" over four assessment sessions

10.3.2 Treatment study results

10.3.2.1 Participants

Twenty-seven patients with MND were recruited for the treatment study in Auckland (8), Christchurch (7) and New York City (12). Three of these participants were excluded because they did not meet the inclusion/exclusion criteria, as two reported no symptoms of dysphagia

and the other reported that they obtained the majority of their nutrition through a PEG tube. Two participants withdrew from the study following screening but prior to the initial assessment. Three participants dropped out prior to or during treatment due to unrelated illness in two participants (kidney stones and influenza) and reported discomfort sitting during the treatment for one participant who usually remained supine. Nineteen participants completed the two-week treatment protocol; however, one of these participants was unable to be contacted for the final assessment due to reported hospitalisation for oral ulcers.

The following data are from the 19 participants who completed the treatment aspect of the protocol (table 10.1). One participant was Spanish speaking and completed the Swal-QOL, EAT-10 and ALSFRS-R in Spanish with a Spanish speaking researcher (Burgos et al., 2012; Campos et al., 2010; Zaldibar-Barinaga et al., 2013). Three participants were unable to consistently complete 80 swallows per treatment session due to fatigue, these participants completed a minimum of 50 swallows in each session. No patient developed pneumonia during the study.

Table 10.1. Demographic information

	Christchurch (n = 4)	**Auckland (n = 7)**	**New York City (n = 8)**	**Total (n = 19)**
Age (years)				
Mean ± sd	66 ± 8	65 ± 9	66 ± 8	66 ± 8
Gender				
Male	1 (25%)	6 (86%)	5 (63%)	10 (53%)
Female	3 (75%)	1 (14%)	3 (38%)	9 (47%)
Diagnosis				
ALS	4	4	8	16
PLS	0	3	0	3
Time since diagnosis (months)				
Mean ± sd	43 ± 51	66 ± 73	20 ± 21	38 ± 47
Range	7 - 159	2 - 122	2 - 57	2 - 159
Medications				

Riluzole	1	3*	1	5
Neudexta	0	0	2	2
MoCA				
Mean ± sd	25 ± 2	27 ± 2	25 ± 2	26 ± 3
EAT-10				
Mean ± sd	13 ± 7	8 ± 7	20 ± 6	14 ± 10
ASLFRS-R				
Mean ± sd	36 ± 10	36 ± 10	31 ± 10	34 ± 12

*One participant stopped taking Riluzole between assessments one and two due to nausea

10.3.2.2 Reliability

Inter-rater and intra-rater reliability is detailed in table 10.2. Measures of inter-rater and intra-rater reliability were excellent for the TWST and TOMASS, except for the measures of inter-rater reliability for the number of swallows for the TOMASS, which was moderate (table 10.2). For measures of CSA of submental muscles measured via US, inter- and intra-rater reliability were moderate to good. Measures of inter-rater and intra-rater reliability of hyoid excursion measured by US were moderate. Hyoid displacement on VFSS was measured with excellent inter-rater reliability and moderate intra-rater reliability. Measures of inter-rater reliability of UES opening distance and pharyngeal constriction ratio were poor; but both measures had good intra-rater reliability. Measures of OPTT and TPTT had moderate inter-rater and good intra-rater reliability. Good inter-rater reliability and excellent intra-rater reliability were found for measures of HPTT. Measures of supraglottic closure timing and UES opening duration had poor inter-rater and moderate intra-rater reliability. Measures of airway closure duration had moderate inter-rater reliability and good intra-rater reliability. For the PAS, 81% of values were scored the same by two separate raters, with a Kappa statistic of 0.044. When analysing the same videos twice by one rater, 89% of values were scored the same, with a Kappa statistic of 0.507.

Table 10.2. Inter-rater and intra-rater reliability of all outcome measures.

Measure	Inter-rater ICC (95% CI)	Rater effect p-value	Intra-rater ICC (95% CI)	Rating effect p-value
TWST volume per swallow	94.83 (82.7-98.4)	.13	98.96 (96.9-99.7)	.315
TWST time per swallow	97.55 (92-99.2)	.45	99.15 (97.6-99.7)	.274
TWST volume per second	[99.77 (99.2-99.2)]	.21	99.5 (98.6-99.8)	.163
TOMASS bites	[99.43 (98.3-99.8)]	.33	[100 (100-100)]	1
TOMASS masticatory cycles	97.6 (93.3-99.2)	.35	99.78 (99.4-99.9)	.203
TOMASS swallows	73.6 (40.2-90.1)	.164	[99.51 (98.6-99.8)]	.757
TOMASS time	[97.98 (94-99.3)]	.24	99.98 (99.9-100)	.75
CSA of LAB	66.61 (23.6-97.5)	.25	55.92 (14-82.7)	.174
CSA of RAB	48.58 (1.7-78.9)	.028*	71.01 (31.3-91.1)	.248
CSA of GH^+	76.21 (44.7-90.8)	.91	83.43 (60.4-94.2)	.341
Hyoid excursion (US)	65.76 (51.6, 76.3)	.01*	70.45 (61.8-78.7)	.103
Hyoid excursion (VFSS)	90.21 (83.8,94.3)	< .01*	73.47 (62.5-82.3)	.351
UES opening distance	46.67 (27.9,64.6)	< .01*	78.07 (70.1,86.0)	.583

PCR	48.85(23.5,72.7)	< .01*	82.69 (74.7-89)	< .01*
OPTT	[57.21 (40.9,70.3)]	.47	[86.81 (80.5-91.8)]	.025*
HPTT	81.36 (72.6,88.2)	.10	90.13 (85.2-93.9)	< .01*
TPTT	[65.4(51.1,77)]	.26	87.68 (81.6-92.2)	.14
Supraglottic closure timing	[0.00 (0.00,21.0)]	< .01*	51.55 (35.7,66.4)	.04*
Airway closure duration	55.79 (38.9,71)	.03*	84.25 (77-89.9)	< .01*
UES opening duration	45.31 (26.2,63.7)	< .01*	60.41 (45.6-73)	< .01*

ICC = intraclass correlation coefficient, CI = confidence interval, * = statistically significant at the .05 level, [ ] = assumptions not met – interpret results with caution.

10.3.2.3 Skill learning

There was no significant effect of trial on the model for temporal (χ^2 [9] = 5.99, p = .741) or amplitude (χ^2 [9] = 5.91, p = .75) error for the skill training task; therefore, trial was not included in the final models. As data for both error types did not meet the assumptions for parametric testing, non-parametric statistics were used. There was a significant difference between assessments for temporal error (χ^2 [2] = 9.38, p < .01). Post-hoc analyses demonstrate that median temporal error decreased from 0.82 s in assessment two, to 0.55 s in assessment three (V = 180, p < .01), with no significant change to 0.53 s at assessment four (p = .77). Median amplitude error also decreased from 11.8 µV in assessment two to 7.28 µV in assessment three (V = 144, p = .05), with no significant change to 7.73 µV in assessment four (V = 61, p = .31).

10.3.2.4 Swal-QOL

The Swal-QOL was incomplete on two assessments of one participant and one assessment of a second participant; thus, data from these time points were not included in the analyses. Data

from all measures of the Swal-QOL met the assumptions for parametric testing. There were no significant effects of assessment session for oral, pharyngeal or secretion symptom frequency. There was a significant effect of assessment session for the Swal-QOL total symptom frequency score (χ^2 [3] = 7.94, p = .047). The average total score was 5.59 points higher in assessment three than in assessment two (95% CI [-0.22, 11.4], p = .017). There was no significant difference between assessment one and assessment two (95% CI [-10.23, 1.62], p = .068) or assessment three and assessment four (95% CI [-5.96, 5.85], p = .982). To further probe the data, an analysis was also completed investigating the amount of change in Swal-QOL score. There was a significant difference between the baseline, treatment and follow-up periods for amount of change in the total score (χ^2 [2] = 7.125, p = .028). Change in Swal-QOL total score was significantly greater over the treatment period than over the baseline period (V = 29, p = .023; figure 10.24). The amount of change in Swal-QOL total score was not significantly different over the baseline and follow-up periods or over the treatment and follow-up periods (p > .05).

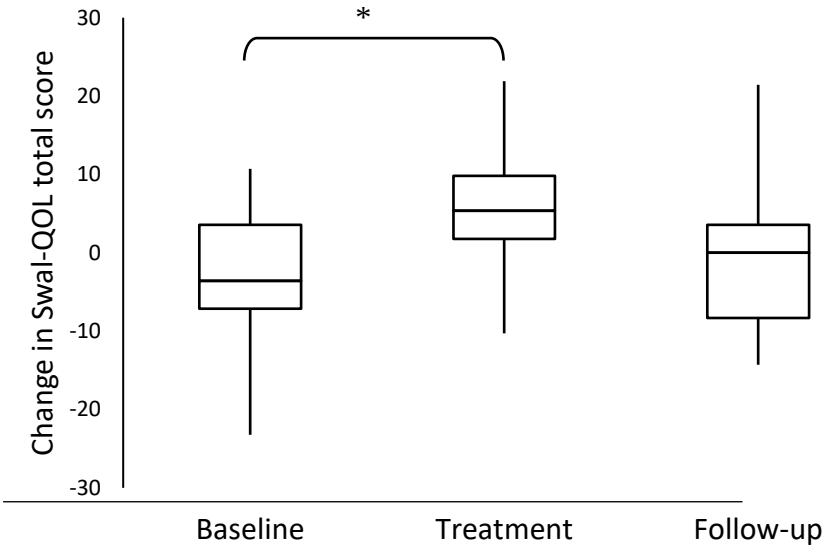

Figure 10.24. Boxplots of the median change in Swal-QOL total score over the three periods. Centre line denotes the median, horizontal lines represent upper and lower quartiles of the data, vertical whiskers represent 1.5 times the interquartile range * = significant change between assessments at the p = .05 level.

10.3.2.5 VFSS structural displacement measures

For the evaluation of outcomes with VFSS, in 6% of swallows, at least one timing measure, and in 4% of swallows, one spatial measure, were unable to be analysed due to participant movement, positioning or the timing of onset of imaging.

For VFSS measures, data met the assumptions for parametric testing for UES opening distance (water, puree and cracker), PCR (water and cracker), hyoid displacement (water, puree and cracker), supraglottic closure timing (water) and UES opening duration (water and puree). Data from other VFSS outcome measures did not meet the assumptions of normality and equality of variance. None of the data investigating difference in amount of change over the baseline, treatment and follow-up periods met the assumptions of normality and equality of variance. Therefore, data from these outcome measures were analysed using non-parametric statistics.

Pharyngeal constriction ratio.

There was a significant effect of assessment on PCR with water boluses (χ^2 [3] = 7.18, p = .066). However, post-hoc analyses showed no significant differences between any of the comparisons of interest (p > .05). There was a significant difference in amount of change in PCR between baseline, treatment and follow-up periods for cracker boluses (χ^2 [2] = 5, p = .082). Post-hoc analyses demonstrated no significant differences in the amount of change in the comparisons of interest (p > .05).

Hyoid excursion.

There was no significant main effect of bolus on hyoid excursion (χ^2 [2] = 0.704, p = .703). Hyoid displacement for puree boluses varied over assessment sessions (χ^2 [3] = 21, p < .001). For puree boluses, mean hyoid displacement was 3.3 mm less in assessment one when compared to assessment two and 2.9 mm greater in assessment four compared to assessment three (table 10.3.). Hyoid displacement was 1.6 mm greater in assessment three than assessment two; however, this change was not statistically significant (table 10.3.). Over the baseline, treatment and follow-up periods, there was a significant difference in the amount of change of hyoid displacement for puree boluses (χ^2 [2] = 5.091, p = .078). Over the baseline period, hyoid displacement reduced by a median of -5.73 mm. Over the follow-up period, median hyoid displacement increased by 2.5 mm; this was significantly greater than the

amount of change over the baseline period (V = 6, p = .014). There were no significant differences between the amount of change in hyoid excursion between the baseline and treatment periods or between the treatment and follow-up periods (p > .05).

Table 10.3. Change in hyoid excursion across assessments with a puree bolus

Assessments compared	Average hyoid excursion
2-1	-3.34 (95% CI [-5.97, -.71], p = .001) **
3-2	1.69 (95% CI [-0.93, 4.32], p = .1)
4-3	2.84 (95%CI [.26, 5.43], p = .006) **

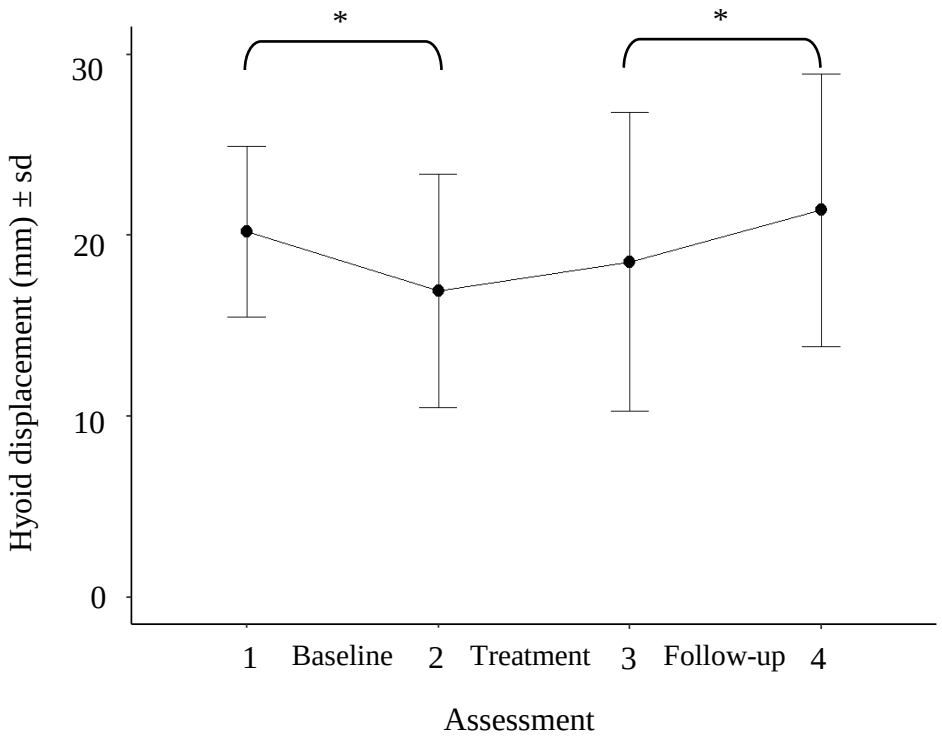

Figure 10.25. Hyoid displacement measured by VFSS over assessment sessions for puree boluses. Vertical lines represent one standard deviation from the mean. * = significant change between assessments at the p = .05 level.

There was a significant effect of assessment session on hyoid displacement for water boluses (χ^2[3] = 8.42, p = .038). Hyoid displacement was 2.4 mm greater in assessment four than in assessment three; there were no significant changes between other assessments of interest

(table 10.4.). No significant differences were observed in the amount of change in hyoid displacement over the baseline, treatment and follow-up periods for water boluses ($p > .1$).

Table 10.4. Change in hyoid excursion across assessments with a water bolus

Assessments compared	Average hyoid excursion
2-1	-1.18 (95% CI [-4.1, 1.73], $p = .301$)
3-2	.82 (95% CI [-2.12, 3.76], $p = .476$)
4-3	2.4 (95% CI [-0.56, 5.36], $p = .04$)**

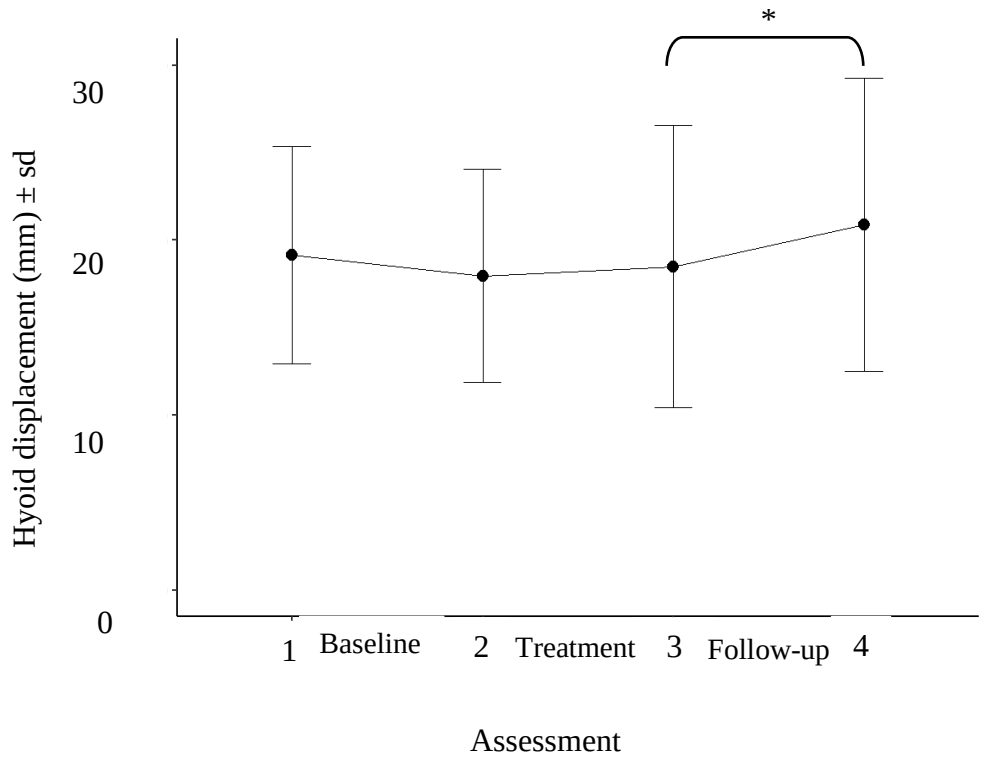

Figure 10.26. Mean hyoid displacement between assessment sessions for water boluses. Vertical lines represent one standard deviation from the mean. * = significant change between assessments at the p = .05 level.

10.3.2.6 VFSS timing measures

A significant main effect of assessment session was observed for OPTT with a water bolus (χ^2 [3] = 9.28, $p = .026$). Median OPTT was 0.32 s at baseline and increased significantly (V

= 7, p = .019) to 0.37 s in the assessment two. There were no significant differences in other comparisons of interest (p > .05). There was a significant difference in the amount of change in OPTT between baseline, treatment and follow-up periods (χ^2[2] = 8.909, p = .012). The amount of change in OPTT for a water bolus was significantly greater during the treatment period than during the baseline (V = 10, p = .042) and follow-up periods (V = 61, p = .01). No significant difference was observed in the amount of change between the baseline and follow-up periods (V = 38, p = .7).

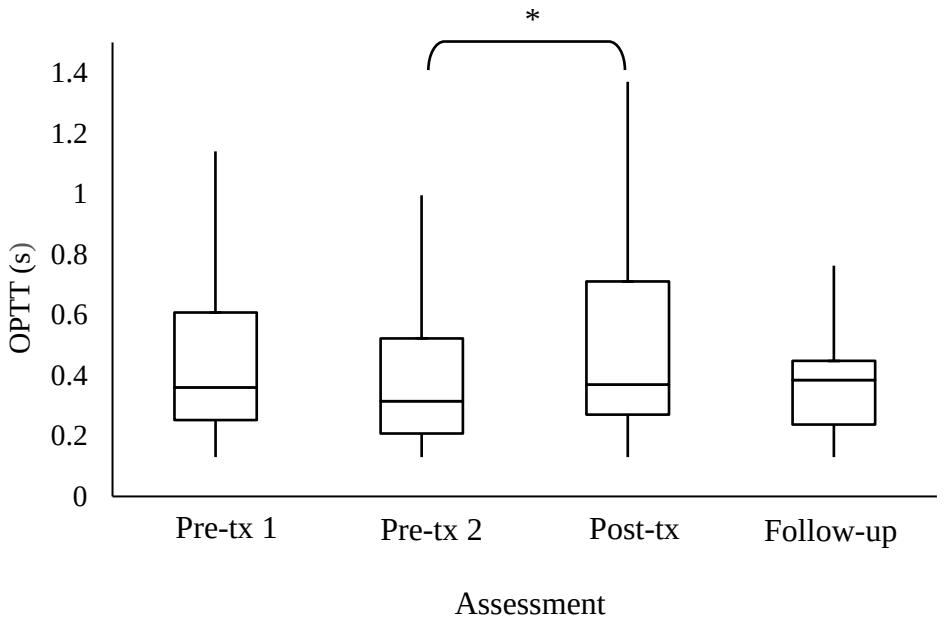

Figure 10.27. Boxplots of the median oropharyngeal transit time for water boluses. Centre line denotes the median, horizontal lines represent upper and lower quartiles of the data, vertical whiskers represent 1.5 times the interquartile range. * = significant change between assessments at the p = .05 level.

There was a significant difference between assessment sessions for OPTT with a puree bolus (χ^2 [3] = 9.33, p = .025). Median OPTT was 0.58 s at assessment one, increased to 1.03 s in assessment two (V = 58, p = .024), decreased to 0.37 s in assessment three (V = 61, p = .01) and had no significant change to 0.39 s at assessment four (V = 40, p = .01). There was a significant difference in the amount of change in OPTT over baseline, treatment and follow-up sessions (χ^2 [2] = 7.818, p = .078). Post-hoc analyses showed no significant difference in the amount of change in oropharyngeal transit time over the comparisons of interest (p > .05).

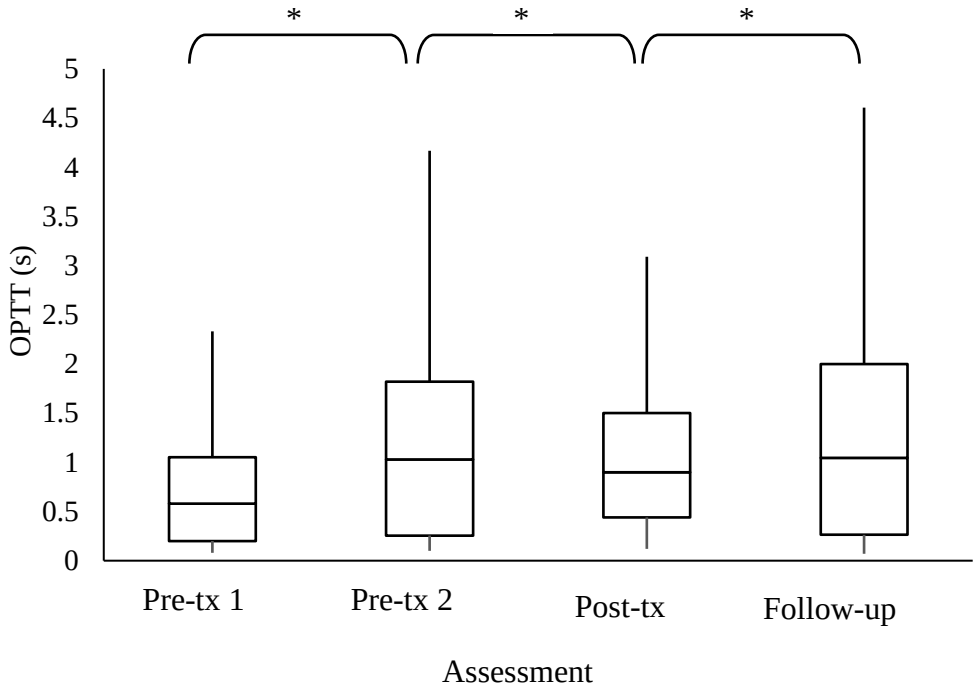

Figure 10.28. Boxplots of the median oropharyngeal transit time for puree boluses. Centre line denotes the median, horizontal lines represent upper and lower quartiles of the data, vertical whiskers represent 1.5 times the interquartile range. * = significant change between assessments at the p = .05 level.

A significant difference between assessments was observed for TPTT of a water bolus (χ^2[3] = 7.08, p = .07). For water boluses, median TPTT decreased from 0.89 s at assessment one, to 0.85 s in assessment two but this change was not statistically significant (V = 37, p = .765). TPTT then increased to 0.96 s in assessment three (V = 6, p = .018) with a decline to 0.88 s in assessment four (V = 40, p = .044). There was a significant difference in the amount of change in TPTT (water) over the baseline, treatment and follow-up condidtions (χ^2[2] = 5.628, p = .06). Post-hoc analyses demonstrated a significantly greater amount of change during the treatment period than during the follow-up period (p = .014). The amount of change was not statistically different between the baseline period and the treatment period (p > .278).

There was a significant difference between assessments for TPTT of a puree bolus (χ^2[3] = 7.04, p = .071). Median TPTT (puree) was 1.35 s at assessment one, increased to 1.76 s in assessment two (V = 59, p = .019), decreased to 1.53 s in assessment three (V = 64, p = .003) and increased to 1.8 s in assessment four (V = 60, p = .014). A significant difference was

observed between baseline, treatment and follow-up periods for the amount of change in TPTT (puree) ($\chi^2[2] = 5.091$, $p = .078$); however, post-hoc analyses showed no significant differences in the comparisons of interest ($p > .05$). There were no significant effects of assessment session on other VFSS outcome measures ($p > .1$; see appendix for details).

10.3.2.7 PAS

All participants had a PAS below three on the initial assessment. There was little change observed in penetration aspiration scale scores over assessments for water, puree or cracker boluses (tables 10.5 - 10.7).

Table 10.5. PAS scores for water boluses of all participants over the four assessment sessions

	PAS SCORE					
	NA	1	2	3	4	5+
Pre-tx 1	0	27	6	0	0	0
Pre-tx 2	0	27	5	0	1	0
Post-tx	0	29	4	0	0	0
Follow-up	0	29	4	0	0	0

Table 10.6. PAS scores for puree boluses of all participants over the four assessment sessions

PAS SCORE						
	NA	1	2	3	4	5+
Pre-tx 1	0	30	3	0	0	0
Pre-tx 2	2	27	4	0	0	0
Post-tx	0	27	6	0	0	0
Follow-up	0	31	2	0	0	0

Table 10.7. PAS scores for cracker boluses of all participants over the four assessment sessions

	PAS SCORE					
	NA	1	2	3	4	5+
Pre-tx 1	4	29	0	0	0	0
Pre-tx 2	0	31	2	0	0	0
Post-tx	2	30	1	0	0	0
Follow-up	1	32	0	0	0	0

10.3.2.8 Ultrasound

Errors occurred in saving the videos for one session with one participant. For the evaluation of hyoid excursion using US, 1% of videos were unable to be analysed due to patient movement or poor positioning of the transducer. One participant was unable to complete the full assessment due to fatigue and therefore does not have a full dataset of US measures. US images of cross sectional area of at least one of the submental muscles were not of sufficient quality for analysis in 7% of assessments.

Hyoid excursion and CSA of GH^+ data met the assumptions required for parametric testing. CSA of LAB and CSA of RAB data did not meet the assumptions of normality and equality of variance, therefore, non-parametric testing was used for these variables. There were no significant effects of assessment session for any of the US data ($p > .1$; see appendix for details). There were no significant differences in the amount of change over the baseline, treatment and follow-up periods for any of the data obtained using US ($p > .1$).

10.3.2.9 TWST and TOMASS

Due to overt signs of aspiration, it was deemed unsafe for two participants to complete the TWST and for one participant to complete the TOMASS. Errors occurred with saving the videos for three assessments, and data could not be extracted offline. For these sessions, the data collected during the sessions were included in the analyses.

Time per swallow data from the TWST met the assumptions for parametric testing. Data from all other TWST and TOMASS measures did not meet assumptions of normality and

equality of variance and were, therefore, analysed with non-parametric statistics. There were no significant differences between assessment sessions for any of the measures of the TOMASS or TWST ($p > .1$; see appendix for details).

10.3.2.10 Pharyngeal manometry

Pharyngeal manometry was attempted with the four Christchurch participants. None of these patients tolerated this assessment due to high levels of discomfort and/or vomiting. Consequently, no manometry data were analysed.

10.4 Discussion for Treatment Studies

This is the first research to evaluate the potential of skill training to improve, or maintain, swallowing outcomes for patients with MND. The studies showed that patients with mild to moderate dysphagia are able to successfully participate in this treatment. This was demonstrated by a low rate of drop out and few patients reporting significant fatigue as a result of the treatment. The patients who did experience difficulty were those in the later stages of the disease with limb and respiratory complications that limited comfortable sitting for prolonged times. Following four weeks of training during the pilot study, patients with mild to moderate dysphagia demonstrated evidence of functional swallowing improvement, indicating that further investigation was warranted. Therefore, the aims of the treatment study were to explore the functional and biomechanical changes to swallowing associated with skill training in patients with MND in a larger cohort. There was no evidence of functional change to swallowing after the shorter two-week training period in this treatment study. However, subtle signs of improvement in swallowing biomechanics and quality of life were identified (increase in hyoid excursion, decrease in oropharyngeal transit time and increase in reported total symptom frequency) that provide justification for further investigation. The information gleaned from this treatment study is a crucial early step in evaluating the effects of skill training for patients with MND.

10.4.1 Pilot study

All participants completed the four-week treatment protocol in the pilot study with no evidence of adverse effects, demonstrating that swallowing skill training is a suitable treatment approach for patients with MND. The study originally aimed to recruit 6 to 10 participants in the Canterbury region. Recruitment of this number of participants was not

possible and the recruitment region was, therefore, expanded within the pilot study. Only two participants from Christchurch, two participants from Auckland and one participant from Wellington were recruited over the twelve months that recruitment was open, indicating that the recruitment area would need to be further expanded to conduct a study with a larger cohort. Inability to travel to the research clinic on a daily basis was reported to be one factor that limited an individual's ability to enrol in the study. Previous research has also documented travel distance as a limiting factor for participation in multidisciplinary clinics for patients with MND (Stephens, Young, Felgoise, & Simmons, 2016). It is therefore crucial in developing treatment approaches for this population that they can be conducted in a patient's home. This led to the decision to facilitate at home treatment as an option for patients in the treatment study. In the pilot study, Pt1 was the only participant to complete part of the treatment independently at home. All sessions were completed by this participant; however, number of swallows per session varied, resulting in an average adherence of 84%. Pt1 reported completing some treatment sessions whilst sitting in front of the television, it is assumed that levels of concentration on the task were less for this participant than other participants who did not have distractions in the room. Clinician presence has been reported as a factor that increases adherence to the treatment protocol and would help to reduce distraction during participation (Krekeler, Broadfoot, Johnson, Connor, & Rogus-Pulia, 2018; Smith-Tamaray, Wilson, & McAllister, 2011). The pilot study reinforced the importance of researcher presence when participants were completing the task, to reduce distractions and ensure that participants complete the required daily number of trials according to the treatment protocol. Therefore, a researcher was present for all sessions performed at home or in the research lab during the treatment study.

Patients with MND demonstrate reduced functional swallowing as measured by the TWST (Hughes & Wiles, 1996). Scores outside normal limits were observed for all participants in assessment one of the pilot study. Functional swallowing outcomes, measured by the TWST, were expected to improve following treatment. The TWST indicated functional improvement in swallowing post-treatment for the three participants with mild to moderate dysphagia. These changes were clinically significant as Pt1 and Pt2 went from outside normal limits before treatment to within normal limits following treatment for at least one aspect of the TWST, and rate of decline appeared to stabilise for Pt3. Improvement in sequential liquid swallowing as a result of skill training with the BiSSKiT software has previously been

observed in patients with neurodegenerative diseases (Athukorala et al., 2014; S. E. Perry et al., 2018).

Findings from the pilot study further shaped the treatment study as it assisted with selection of outcome measures. Previous research demonstrated that US is a valid method of measuring CSA of submental muscles (Macrae et al., 2013) with moderate to good intra-rater reliability and moderate intra-rater reliability (Winiker, 2019). Additionally, measures of hyoid excursion obtained using US have been shown to have good to excellent intra-rater reliability and moderate to good inter-rater reliability in healthy participants (Hsiao et al., 2012; Macrae et al., 2012) and patients with dysphagia (Y.-C. Chen, Hsiao, Wang, Fu, & Wang, 2017). During the pilot study, researchers did not gather US videos that were of high enough quality for reliable offline measurement, highlighting limitations with the methods and/or knowledge of the researchers obtaining the images. Poor reliability of measurement for ultrasound images in the pilot study suggested that further training to increase the quality of images was required before implementing the treatment study. It also encouraged the researchers to perform online measures during assessment sessions to ensure high quality videos were captured. Ultrasound was only utilised in three participants in the pilot study because the instrumentation was not portable, so could not be taken to patients outside of Christchurch. This highlighted the necessity of using portable ultrasound instrumentation in the treatment study that was conducted across three locations.

When originally designed, this research series was going to be included as part of a larger study that included investigation of speech outcomes. Although we speculated a potential for transference across tasks (Kleim & Jones, 2008), there did not appear to be an effect of skill training for swallowing on measures of speech in patients with MND. The rate of decline in speech tasks remained stable across all participants, regardless of the presence or absence of treatment. It is likely that the speech assessments were too far removed from the trained skill for transference to these tasks to occur. Prior to commencement of the treatment study, it was revealed that the larger, collaborative study would no longer proceed. Therefore, as there was a lack of transference observed from the swallowing training to speech and voice tasks during the pilot study, the scope of the treatment study was refined and did not include investigation of speech production.

Quality of life and patient perception of dysphagia were integral aspects of this research as it is known that dysphagia results in reduced quality of life in patients with MND (Paris et al.,

2013). Both the Swal-QOL and EAT-10 surveys were included in the pilot study to align with the aforementioned collaborative study. Scores from the Swal-QOL and EAT-10 assessments varied in the same manner for most participants, and it was therefore concluded that both assessments were not necessary. The Swal-QOL is a validated measure of quality of life that has been shown to differentiate between dysphagic and non-dysphagic patients with ALS (Paris et al., 2013). The EAT-10 was designed as a screening measure for swallowing (Belafsky et al., 2008) and has been shown to have poor ability to detect small changes in swallowing ability (Cordier et al., 2017; Wilmskoetter et al., 2019). It was therefore decided that the Swal-QOL would be a more robust measure of patient-reported quality of life in the treatment study and the EAT-10 was removed.

The TOMASS did not highlight functional changes to swallowing as a result of treatment during the pilot study. This was expected as the oral phase of swallowing contributes to all of the outcomes associated with the TOMASS. All participants in this study experienced oral phase dysphagia to varying degrees and oral phase dysphagia was not addressed by the skill training exercise. Assessment of functional swallowing of solids was an important aspect of this research and as there was no alternative simple and portable exam that could be used, the TOMASS was included in the treatment study.

The pilot study also identified an issue with calibration of the sEMG equipment. Calibration during the pilot study set the skill training trials at 30-70% of a patient's average muscle recruitment for effortful swallows. This was based on previous research that demonstrated that healthy participants performed low effort swallows at 29 - 34% of their maximum effort during effortful swallowing (Ng, 2018). The significant difference in muscle recruitment between regular and effortful swallowing in healthy participants indicates the presence of a functional reserve, a concept that has been frequently reported in the dysphagia literature (Yeates, Steele, & Pelletier, 2010; Youmans, Youmans, & Stierwalt, 2009). It was identified that not all participants in the current study were able to produce effortful swallows with greater submental muscle activation than their normal swallows. This meant that during the task, the target was placed at an amplitude that was lower than what was achievable, and they were consistently overshooting. EMG activity during a maximal voluntary muscle contraction has been demonstrated to be reduced in patients with MND, which may be due to loss of motor units or spasticity (Krarup, 2011). Further, patients with MND do not demonstrate differences in hyoid excursion between different consistencies, demonstrating

reduced ability to spontaneously adapt swallowing in response to bolus properties (Waito, 2019), likely the result of a loss of functional reserve. Loss of functional reserve in patients with MND may have contributed to the patients' inability to perform an effortful swallow at an amplitude that was significantly greater than their normal swallow. This meant that the calibration of the software was such that their normal swallows were often reaching the top of the screen, and individuals had difficulty modifying swallowing to achieve success with lower targets. As discussed in the methods section, for the treatment study, alterations were made to the calibration protocol to counteract this limitation.

This pilot study played an integral role in establishing the treatment study as it highlighted adaptations that were necessary to accommodate this population, such as altering calibration methods and reducing participation time. This allowed greater consistency in treatment provision between participants in the treatment study. Importantly, the pilot study demonstrated functional improvement in the TWST for patients with mild-moderate dysphagia, justifying further research to evaluate potential physiologic and functional changes.

10.4.2 Skill training for patients with MND

For patients with MND, there was, historically, the belief that exercise would lead to increased rate of degeneration and negative health outcomes (Plowman, 2015). However, evidence is emerging that exercise completed at an appropriate intensity may be beneficial (Carreras et al., 2010; Plowman, 2015). No participants in either the treatment or pilot study developed negative swallowing related outcomes over the course of these studies. This suggests that skill-based swallowing training using the BiSSKiT software is a safe and well-tolerated treatment for patients with MND. Over the treatment protocol, participants improved their accuracy at the skilled swallowing task, indicating that the skill training was at an appropriate level to facilitate task improvement. This improvement in accuracy was maintained over the follow-up period of no treatment. Although, the follow-up period was only two weeks post-treatment, maintenance of skill is an important factor that differentiates skill training from strength training. Due to the short time period between treatment and follow-up, this research is not directly comparable to previous research that demonstrated reductions in function 2-6 months following offset of strength training (Cheah et al., 2009; Drory et al., 2001).

10.4.2.1 Quality of life

Quality of life is negatively affected in patients with dysphagia as a result of MND (Paris et al., 2013; Tabor et al., 2016). Changes in quality of life in response to treatment for dysphagia have not been previously investigated in this population. However, two studies investigating limb stretching exercises for patients with MND resulted in improvements in quality of life (Dal Bello-Haas et al., 2007; Drory et al., 2001). There were no significant changes in oral, secretion or pharyngeal Swal-QOL scores when analysed independently. There were high levels of variability observed between participants resulting in large standard deviations, which could have contributed to the lack of significant findings. However, the total symptom frequency as measured by the Swal-QOL demonstrated improvement in score following treatment. Further, in patients with MND, Swal-QOL scores have been demonstrated to be negatively correlated with the penetration aspiration scale as patients who demonstrate aspiration on VFSS score lower on the Swal-QOL (Tabor et al., 2016). The change in score over the treatment period was significantly different to the change in score over the baseline period, over which quality of life declined. This is in contrast to previous research investigating skill training in patients with Parkinson's disease that demonstrated an improvement in quality of life over an initial baseline no treatment period as well as during treatment itself (Athukorala et al., 2014). The difference between direction of change over the baseline and treatment periods seen in the current research helps to reduce the likelihood of the observed change being a result of a placebo effect; however, as there was no control group this cannot be ruled out.

10.4.2.2 Structural displacement

Hyoid excursion is an important aspect of swallowing as it facilitates epiglottic deflection and UES opening. Over the no treatment baseline period in this study, the extent of hyoid excursion decreased but not to the level of statistical significance. This mirrors previous research in this population (Plowman, Watts, Tabor, et al., 2016) and is likely due to the rapidly degenerative nature of MND.

Hyoid excursion increased following training, both in this study and in previous research investigating EMST (Plowman, Watts, Tabor, et al., 2016). The reasons for increased hyoid excursion in these studies are likely different due to the underlying nature of the treatments. An increase in hyoid excursion following EMST is hypothesised to be due to strengthening of

the submental muscles during treatment (Plowman, Watts, Tabor, et al., 2016). The current treatment focused on increasing swallowing skill and not strength. An increase in peripheral muscle strength occurs as a result of exercises that are conducted above the habitual level (Rasch & Morehouse, 1957; Zatsiorsky & Kraemer, 2006). During skill training sessions, participants swallowed at 40 – 70% of their maximum power output, which would be not be expected to above their habitual level (Ng, 2018). Further, as there was no evidence of hypertrophy of submental muscles as measured by US, we would not expect an increase in strength of submental muscle contraction to account for the observed changes in hyoid excursion.

The relationship between muscle strength and structural displacement during swallowing is inconclusive in the literature. The submental muscles contribute to hyolaryngeal excursion as well as jaw opening, and therefore, it would be assumed that jaw opening strength would be correlated with hyoid excursion during swallowing. It has been demonstrated in healthy elderly men that jaw opening force is positively correlated with hyoid resting position but not hyoid position at maximum excursion (Shinozaki et al., 2017). In healthy elderly women, there were no significant correlations between submental muscle strength measured by jaw opening and any of the assessed measures of hyoid position (Shinozaki et al., 2017). The relationship between coordination and extent of movement of the hyoid bone has not been fully examined. Using 2D kinematic swallowing motion analysis, Paik et al. (2008) demonstrated different patterns of hyoid displacement between healthy controls, patients with myopathy and patients with supratentorial stroke. The authors hypothesised that they would observe weakness in patients with myopathy, whereas reduced coordination with or without weakness would be observed in patients following stroke. The stroke patients demonstrated irregular velocities and extraneous anterior and posterior movement of the hyoid bone, which were not observed in the other groups, suggesting the presence of incoordination contributing to a change in hyoid bone displacement. A further study investigated the relationship between hyoid trajectory and submental muscle strength and precision in seven patients with dysphagia following stroke (Ng, 2018). Hyoid trajectory was radiographically visualised, submental muscle strength was measured through sEMG of effortful swallowing and a maximum jaw opening task; submental muscle precision was measured through a skilled swallowing task, similar to that used for treatment in the current research and a skilled jaw opening task. Hyoid trajectory was not found to be significantly associated with either strength or skill of the submental muscles in the tasks assessed (Ng, 2018). Further research

investigating the effects of impaired skill on hyoid trajectory is necessary in advancing treatment options for patients with dysphagia.

In the limb literature, skill learning has been shown to result in neuroplasticity (Pascual-Leone et al., 2005; Tyč et al., 2005) and transference of the skill to similar behaviours (Kleim & Jones, 2008). Skill acquisition was evidenced in this swallowing task by a reduction in errors over the treatment period. It is, therefore, possible that this skill training task resulted in neuroplasticity, allowing greater cortical control of swallowing and increased coordination of recruitment of the muscles involved in hyolaryngeal excursion. However, neural imaging studies are required to confirm or deny this speculation.

There was no significant improvement in hyoid displacement immediately following the treatment period. However, there was a trend towards improvement for both thin and puree bolus types. The sample size of patients who received VFSS was small (n = 11) and the standard deviation was large for this measure. A larger sample size and/or more homogeneous population may have increased the ability to detect a significant change in hyoid excursion immediately following treatment. Interestingly, significant improvements in hyoid displacement measures were observed over the follow-up period for both water and puree boluses. Improvements in swallowing outcomes over a non-contact period following swallowing skill training have previously been observed in patients with Parkinson's disease (Athukorala et al., 2014). This may suggest that swallowing skill-learning occurs both online and offline, and neural adaptation continues to occur throughout the late stages of training and periods of skill consolidation and retention (Kida, Sakimoto, & Mitsushima, 2017; Luft & Buitrago, 2005; Spampinato & Celnik, 2017). Curtis and colleagues (2020) investigated the effects of respiratory swallow coordination training in a single patient with anoxic brain injury. The patient completed one treatment session per week for four weeks. Frequency of optimal respiratory swallow pattern was observed during the probe task and a generalisation task in which various consistencies were ingested. Improvement in frequency of optimal respiratory swallow pattern was found as a result of training, with further improvements observed following a one month retention period on the generalisation task. The same pattern of improvement was not seen for the trained task, with improvements demonstrated over the training period but not the follow-up (J. A. Curtis, Seikaly, et al., 2020). This indicates improvement in generalisation over a period of no treatment following a swallowing skill training protocol, as was observed in the current study. It is therefore possible that in the

current study improvement was demonstrated over the follow-up period due to increased time necessary for transference of the learned skill to untrained tasks such as bolus swallows during VFSS. This transference to the TWST, a functional swallowing task, was not observed in the treatment study. This may be due to the task being further removed from the trained task as sequential swallows are required during the TWST. Further discussion regarding functional swallowing outcomes is presented below.

Transference to untrained tasks over the follow-up period may be contributed to by mental practice, defined as the cognitive rehearsal of physical movements. In the limb literature, mental practicw has been shown to facilitate cortical plasticity (Page, Szaflarski, Eliassen, Pan, & Cramer, 2009) and improve functional outcomes when compared to traditional treatment approaches alone (Page, Levine, & Leonard, 2005; Page et al., 2009). In an FMRI study, Page and colleagues (2009) demonstrated increased activation in the premotor area and primary motor cortex following 10 weeks of mental practice in patients with chronic stroke. The tasks were activities of daily living that involved the effected arm of the patients. In addition to increased cortical activation, the authors report anecdotal evidence of transference to tasks that were not included in the treatment programme. Motor imagery and mental practice results in activation of cortical areas associated with motor movements, including the primary motor cortex, premotor cortex and the posterior parietal lobe (Hanakawa et al., 2003; Kosslyn, Ganis, & Thompson, 2001). In the current study, many patients reported thinking about the skill training task when not in the treatment sessions and may, therefore, may have been subconsciously using this mental practice technique outside of the treatment sessions and in the two weeks of no treatment during the follow-up period. Continued mental practice during the follow-up period may have contributed to continued cortical adaptation, resulting in the observed significant changes over the final period of no treatment. Functional improvements resulting from mental practice have not been investigated in patients with MND; however, in chronic stroke patients, the addition of mental practice to physical practice of functional tasks using the hand resulted in improved outcomes that were not observed with physical practice alone (Page, Levine, & Leonard, 2007; Page et al., 2005). In healthy adults, mental imagery of swallowing has been shown to activate areas of the brain that are comparable to those activated during swallowing, including the precentral gyrus and inferior frontal gyrus (Kober, Grössinger, & Wood, 2019). A recent study investigated the use of mental practice to increase lingual strength in a small cohort of healthy older individuals (Szynkiewicz et al., 2020). Improvements in maximum isometric press and

pressure during regular effort saliva swallowing were observed for the group who underwent physical exercise and mental practice but not the control group, a group who did mental practice alone or the group who did physical exercise alone. Although this is early research in healthy individuals, it highlights the potential benefits associated with mental imagery for swallowing.

Another possible explanation for the observed increase in hyoid excursion is a reduction in tone of the submental muscles. Spasticity in MND is a result of UMN damage and can affect bulbar muscles as demonstrated by spastic dysarthria (Darley et al., 1969; R. M. Miller & Britton, 2011). SEMG as biofeedback has been used as a method for reducing spasticity and improving function through targeted relaxation of specific muscles (Dursun, Dursun, & Alican, 2004; Marchant, McAuliffe, & Huckabee, 2008; Nash, Neilson, & O'Dwyer, 1989). In the current research, many participants anecdotally reported that the most difficult targets to hit were the lower targets, as they had difficulty down-regulating the effort involved in the swallowing task. Participants often had to attempt to relax the submental muscles during swallowing to achieve success at the lower targets. Additionally, participants were asked to hold the muscles still between swallowing trials, with the line from the sEMG remaining at the bottom of the screen. This was not monitored and no verbal feedback was given to participants regarding their success; however sEMG feedback of the submental muscles was provided. It is therefore possible that although it was not a direct target of this treatment, there was an element of relaxation training of the submental muscles, resulting in reduced underlying tone. The presence of muscle spasticity was not assessed in these patients; this may explain why there was not consistent improvement over all individuals. As previously discussed, there was no immediate change in response to treatment. It would therefore be hypothesised that spasticity continued to decrease over the non-contact period or that the reduction in spasticity was better incorporated into bolus swallowing over this time. As spasticity was not assessed it is difficult to conclude whether this contributed to the outcomes.

As well as VFSS, hyoid displacement was also measured using US; however, a significant increase was not identified using this technique. There was a difference in the number of participants in each group, as only the participants in NZ underwent VFSS, but all participants underwent US. If both measurements were equal and there was a true effect it is more likely that this would be statistically significant with a larger sample size, due to the

positive relationship between sample size and statistical power (Dupont & Plummer, 1990; VanVoorhis & Morgan, 2007). However, this was not the case, indicating that the differences in significance between the two modalities were likely due to the imaging techniques themselves. Intra-rater reliability of hyoid displacement was higher with images obtained using VFSS than with US. Higher reliability implies that variance is lower and the effect sizes are increased, thereby increasing the power to detect a significant difference (Humphreys, 1993; Kanyongo, Brook, Kyei-Blankson, & Gocmen, 2007).

In healthy individuals, almost complete obliteration of the pharynx would be expected during swallowing (Kendall et al., 2000). Increased pharyngeal constriction ratio (PCR) is common in patients with MND and has been shown to be associated with pharyngeal residue (Waito et al., 2018). As in previous research, pharyngeal constriction was impaired in most individuals who participated in this study. There was no significant change in pharyngeal constriction ratio as a result of the skill training protocol. PCR has been previously investigated pre- and post-treatment in this patient population with no significant differences found as a result of five weeks of EMST (Plowman, Watts, Tabor, et al., 2016). The differences between outcomes for PCR and hyoid excursion in this study may be due to the fact that the muscles targeted in treatment are not directly involved in pharyngeal closure. This would imply a lack of transference to associated biomechanics following the short training period. Alternatively, the lack of detection of change may be due to the high standard deviations observed within the current study; standard deviations were not reported by Plowman, Watts, Tabor, et al. (2016). Further research with a more heterogeneous sample may help to determine if significant changes to PCR are possible as a result of these treatment modalities.

No significant differences were observed for cracker boluses across any of the outcome measures on VFSS. Bolus size can have a significant effect on swallowing kinematics (Dantas et al., 1990; Nagy, Molfenter, Péladeau-Pigeon, Stokely, & Steele, 2014; Ryu, Park, Oh, Lee, & Kang, 2016). In this study, during VFSS, participants self-selected their bite size of crackers and this was not controlled across assessments. If the size of the bite of cracker had been predetermined and consistent between assessments, it may have allowed more information to be gleaned from these assessments.

10.4.2.3 Swallowing timing

In healthy individuals, swallowing transit time is impacted by bolus consistency, with more viscous consistencies such as puree resulting in a longer pharyngeal transit time than thin liquids (Taniguchi, Tsukada, Ootaki, Yamada, & Inoue, 2008). In patients with MND, the speed of bolus transit through the pharynx is reduced, with progressive decline throughout the disease process (J. Tomik et al., 2017). To date, research has not highlighted treatment options that are effective for increasing pharyngeal transit speed.

Normative data for bolus transit timing have not been established for the 5 cc boluses used in this study. Prior research has documented a significant effect of bolus size on OPTT, but no significant effect of bolus size on TPTT (Kendall et al., 2000). This suggests that referencing existing 1 cc norms is appropriate for liquid boluses for TPTT but not for OPTT. Interestingly, in this cohort, median TPTT was within the range of normal for 1 cc water boluses at baseline and across all subsequent assessments. No normative data have been established for pharyngeal transit times of puree or solid boluses and as pharyngeal transit time is dependent on bolus consistency it is not appropriate to compare puree boluses to normative data for thin liquids.

The direction of change in OPTT and TPTT were the same over the baseline, treatment and follow-up periods, with the same comparisons reaching significance. This is to be expected as OPTT and HPTT make up TPTT. Surprisingly, the direction of change varied between thin liquid and puree boluses, with an increase in OPTT and TPTT following treatment for thin liquid and a decrease for puree. The observed changes in water boluses were contrary to what was hypothesised. Although the oropharyngeal phase of swallowing was significantly slower following treatment for water boluses, the change was only 0.05 s, or approximately one frame. A change of 0.05 s is likely not clinically significant as it did not result in an increase in airway invasion. Further, when many hypotheses are tested within a study it increases the probability of a finding being statistically significant by chance alone (Streiner, 2015). As the patterns of change were not predictive of functional changes, and the direction of change differed between bolus types, it is possible that these findings were spurious. It was determined a priori that adjustments would not be made for multiple comparisons. The reason for this decision was that due to the exploratory nature of this research, the risk of missing a significant finding due to overcorrection would likely be more detrimental than the alternative risk of type I error. If Bonferroni corrections were made for multiple comparisons,

only the decrease in OPTT over the treatment period and increase in OPTT over the follow-up period for puree boluses would remain significant. There is no definition of what would be considered normal transit time for 5 cc puree boluses. However, patients with MND often demonstrate an increase in pharyngeal transit time, which increases over the course of the disease (J. Tomik et al., 2017). Therefore, a reduction in OPTT was considered an improvement in swallowing timing. The significant reduction in OPTT over the treatment period that was observed for puree boluses could be explained by an increase in swallowing skill resulting in increased speed of pharyngeal swallowing initiation. The significant increase during the follow-up period would indicate that these changes were not maintained following the offset of treatment, in patients with this rapidly progressive neurodegenerative disease.

10.4.2.4 Swallowing safety

In this study, PAS did not improve significantly over the course of the treatment; however, the scores were all within normal limits at the time of the initial assessment, likely producing a ceiling effect. Previous research concluded that for patients with MND, an EAT-10 score greater than three had good discriminant ability to identify patients who exhibit penetration and an EAT-10 score greater than eight to identify patients who aspirate (Plowman, Tabor, et al., 2016). This finding was not replicated in this study. There was no evidence of penetration or aspiration during the initial assessment despite all participants having an EAT-10 score ≥ 3 and 13 participants having an EAT-10 score ≥ 8. Further, the only participant who demonstrated trace penetration in the second assessment had a comparatively low EAT-10 score of four. The difference in findings may be due to the bolus sizes that were trialled. In patients with MND, aspiration is more common with thin fluids than puree or solid boluses (D'Ottaviano et al., 2013). In the previous research, participants had thin liquid boluses of varying amounts including a 20 cc bolus and a 90 cc sequential sips task, with analysis of the worst PAS score (Plowman, Tabor, et al., 2016). In the current study, bolus size was limited to 5 cc on VFSS. Therefore, if larger bolus sizes of thin fluid were used we may not have observed this ceiling effect for PAS.

Kappa statistics were used to determine inter- and intra-rater reliability of the PAS. These kappa statistics demonstrated no agreement and weak agreement, respectively, indicating that reliability of the PAS scale may be a limitation of this study. However, the kappa statistic becomes less reliable when one or more of the categories contains occurrences which are rare (Viera & Garrett, 2005). In this study, most participants had a PAS score of 1, leaving the

other categories to be only rarely observed. Therefore, it is important to consider the high percentage agreement of both inter- and intra-rater reliability, 81% agreement and 90% agreement respectively. Inter-rater and intra-rater reliability are therefore likely sufficient for measures of the PAS.

10.4.2.5 Functional swallowing

Although total pharyngeal transit time for a single sip of water was within normal limits, mean scores for all TWST and TOMASS measures were outside normal limits at all assessment points. This inconsistency may be due to the differences in demand between single and sequential sips. In addition to pharyngeal transit time, the TWST and TOMASS are impacted by oral transit time and an increased demand on the respiratory system due to sequential swallowing (Hegland, Huber, Pitts, Davenport, & Sapienza, 2011). As patients with MND often have reduced respiratory capacity, this could have contributed to increased time taken to complete the TWST due to an increased number of pauses between swallows for respiration than would be expected in healthy participants. This irregular pattern of breathing and swallowing has been previously recorded in the literature (Aydogdu, Tanriverdi, & Ertekin, 2011) and would contribute to both the time taken and number of swallows to complete the TWST. Sequential swallowing was not completed under instrumental evaluation so it cannot be confirmed if a similar pattern of disorganised swallowing was present in the individuals who participated in this study.

The degree of change in functional outcomes for participants in the treatment study was not as compelling as what was observed in the pilot study for these assessments. Of the 18 participants who completed the TWST pre- and post-treatment, nine demonstrated improvement in volume per swallow following treatment. However, this change was not statistically significant and there does not appear to be a pattern that predicted improvement, unlike in the pilot study, in which all participants who had mild to moderate dysphagia improved following treatment. One major difference between the pilot study and the treatment study that could have contributed to this variation is the treatment dosage. The pilot study consisted of 20 sessions of skill training compared to 10 in the treatment study. The reason for reducing participation time was feasibility for patient participation and to align this study with previous research that demonstrated significant differences in patient outcomes after two weeks of skill training for patients with Parkinson's disease (Athukorala et al., 2014). However, compared to the study by Athukorala et al. (2014), the number of trials per

session in this study were reduced from 100 to 80. This was to ensure that the intensity of the exercise was not high enough to potentially result in fatigue and negative outcomes that have been associated with higher intensity exercise for patients with MND (Carreras et al., 2010). As sequential swallowing was not directly trained during this task, 10 skill training sessions may not have been sufficient for transference to the TWST. However, it is possible that there are potential benefits for this treatment that were not observed within the treatment study due to the intensity limitations for the MND population.

There were no observed changes in TOMASS outcomes for either the pilot or treatment study. This finding is not surprising, as although pharyngeal swallowing is assessed during the TOMASS, the oral phase of swallowing is an integral aspect. During the TOMASS, the cracker must be manipulated in the oral cavity prior to pharyngeal transfer. This requires adequate strength and range of motion of the muscles required for jaw closing and lingual movement (Huckabee et al., 2017; Morita et al., 2018; Stierwalt & Youmans, 2007). Lingual strength and range of motion as well as bite strength are often some of the first signs of dysphagia in patients with MND (Briani et al., 1998; Higo et al., 2004; Riera-Punet et al., 2018). Some participants in this research had significant oral phase difficulties, and therefore, used their hands to break the cracker as they could not bite it, used their hand to press on their jaw to bite the cracker or softened the cracker in their mouth by sucking it prior to mastication. The skill training protocol used in this research focuses on the onset, timing and amplitude of pharyngeal swallowing and changes in masticatory efficiency would not be expected. It is, therefore, likely that the TOMASS was not specific enough to the trained task to detect functional changes.

10.4.2.6 Pharyngeal manometry

Of the four participants in Christchurch who attempted to complete manometry, none tolerated catheter placement. The observed reduced tolerance is likely due to an increased gag reflex in patients with MND as a result of UMN dysfunction, which has also been observed in studies that implement FEES (Aviv et al., 2002; Brooks, 1994; Cohen et al., 2003; Domer et al., 2013; Leder et al., 2004). The successful use of HRM without impedance has been reported previously in the literature in patients with MND (Suh et al., 2019). In this study limited information was provided about placement methods; however, it was noted that ten percent lidocaine spray was used (Suh et al., 2019). Recent research has demonstrated that topical nasal anaesthetic does not have an effect on comfort during HRM with or without

impedance in healthy participants (Guiu Hernandez et al., 2018; Kwong, 2018). It is therefore unlikely that this was the cause of increased discomfort in the current study population. The diameter of the catheter used in the study by Suh et al. (2019) was not reported; however, as the catheter did not measure impedance, it is likely that the diameter was smaller than in the current study. Healthy individuals tolerate a catheter with a smaller diameter better than a large diameter the first time they undergo HRM (Kwong, 2018). When using the same catheter as in the current research, previous research found that 19% of healthy participants were unable to tolerate catheter placement (Kwong, 2018). It is therefore likely that the large catheter size in conjunction with UMN pathology contributed to the inability to tolerate catheter placement in the four individuals who participated in the current study.

10.4.2.7 Medications

Neudexta is a medication used for patients with MND that contains an antitussive agent (C. P. Taylor et al., 2016). Two participants were taking Neudexta at the time of the study. Neither of these participants underwent VFSS as they were in New York City, so silent aspiration cannot be ruled out. Although it does not guarantee the absence of aspiration, it is important to consider that there was no evidence of aspiration pneumonia throughout the protocol. There was one participant whose medication was altered during the baseline period as Riluzole was discontinued due to the side effect of severe nausea. There is little evidence to suggest significant improvements in swallowing as a result of Riluzole for patients with MND (R. G. Miller et al., 2012) and this participant was not deemed to be an outlier in the amount of change over the period for which he stopped taking the drug, he was therefore, included in the final analysis. For all other participants, medication remained stable, and as a result, the observed effects are not likely due to medication.

10.4.2.8 Cognition

Almost half of all patients with MND have some degree of cognitive impairment, and 10-15% meet the criteria for frontotemporal dementia (Gordon et al., 2011; Ringholz et al., 2005). In this study, seven participants scored outside the normal range (< 26) on the cognitive screening test. However, two participants were unable to complete the full assessment due to impaired hand function inhibiting their ability to use a pen, and therefore, the lower score is not truly reflective of poor cognition. This highlights the need for the development of a cognitive screening tool that is appropriate for patients with MND who

have impaired motor function. Importantly, none of the participants had difficulty following instructions to participate in the treatment sessions, indicating that skill training with a clinician present is feasible for patients with cognitive abilities outside the normal range.

10.4.3 Limitations and future directions

When considering the outcomes of these studies, it is important to acknowledge the limitations. Although some changes in swallowing biomechanics and quality of life were observed, these changes were not compelling, as many outcome measures were investigated in this study without correction for multiple comparisons. It is, therefore, possible that falsely significant changes were observed, given the absence of functional correlation. This was expected due to the exploratory nature of this research; however, further research with a larger sample size would be beneficial to determine whether the observed effects are replicable.

The sample size included in this study was small: 11 participants for VFSS measures, 19 participants in total, and the standard deviations were large. The large standard deviations are likely a result of the heterogeneity of the population and contribute to a reduced ability to detect statistically significant changes. The inclusion criteria for this study were broad to increase the number of potential participants. This would have contributed to the observed large standard deviations. Further, due to the limited sample size, participants acted as their own controls during a baseline no treatment period. There was no control group that underwent a sham treatment to rule out the possibility of a placebo effect. However, as participants in this study have a rapidly degenerative disease, this method did allow for comparison of treatment results to the natural decline seen during the baseline period. This method also allowed a greater number of participants to compete the treatment arm of the study. A sham group would have reduced participants completing the treatment by half, which would have been a greater limitation on the study.

All participants underwent skill training regardless of differences in swallowing biomechanics observed during instrumental assessment. Research has begun to investigate a method of determining if a patient's dysphagia is the result of strength or skill deficit (Ng, 2018). Further developments of this assessment would be beneficial for all patients to ensure that they are receiving the most appropriate treatment approach. It was discovered that many participants lacked the ability to achieve greater activation of the submental muscles during

an effortful swallow compared to normal swallowing. This may be due to a reduced functional reserve resulting in maximal muscle activation during normal swallowing. Participants in this category may have benefitted from a period of strength training prior to skill training to increase strength of submental muscles and allow for greater muscle recruitment during swallowing. Strength training using EMST has been shown to have some potential benefits for patients with MND (Plowman et al., 2019; Plowman, Watts, Tabor, et al., 2016). As there is a large amount of heterogeneity in patients with MND due to the combination of UMN and LMN symptoms, it remains plausible that some individuals with MND would benefit from skill training, whereas strength training or a combined approach may be a better for others. Collapsing all patients into one group based solely on their diagnosis limits potential findings across many areas of research.

The skill that was trained during this treatment was a single saliva swallow every thirty seconds. The task trained did not involve a bolus, and was therefore, not specific to the bolus swallowing outcome measures that were assessed. Patients with MND frequently report anterior loss of saliva as indicated by the ALSFRS-R (Cedarbaum et al., 1999). Excess saliva is due to a reduction in frequency and efficiency of saliva swallowing, and therefore, may have been improved by the treatment task (Bongioanni, 2012; Garuti, Rao, Ribuffo, & Sansone, 2019). The only outcome measure that addressed saliva swallowing was the secretions symptom frequency subscale of the Swal-QOL. This was reported by participants to be the most severely affected aspect of the Swal-QOL; however, there was no significant change as a result of treatment. This measure is made up of the outcomes from only two questions – the presence of thick saliva and the presence of excess saliva. Thick saliva is a common complaint in patients with MND (Newall, Orser, & Hunt, 1996), and would not have been addressed by the current treatment. It is therefore, not surprising that no changes were observed in this outcome measure. Future investigation about saliva swallowing frequency and drooling before and after treatment may be beneficial in determining the effects of the trained task.

Immediately after every trial, feedback was provided to participants regarding the distance from the centre of the target and whether the attempt was successful. Research investigating skill learning in patients following stroke has demonstrated that a delaying feedback for a few seconds and not providing feedback for all trials, instead giving a summary, may enhance learning (Van Vliet & Wulf, 2006; Zimmerman, Carnaby, Lazarus, & Malandraki, 2020). An

alternative feedback schedule may have facilitated greater learning in patients. A potential example of this within the swallowing literature is that used by Martin-Harris and colleagues (2015) when training respiratory swallow coordination in patients with head and neck cancer. In the initial acquisition phase, feedback was provided following all trials; however, when participants moved to the mastery phase they aimed to complete the task without the visual or verbal feedback. In the current research, although the task did become more difficult with skill improvement, the feedback frequency did not change. Further research investigating skill training with a delayed and or less frequent feedback approach may result in improved awareness and therefore control of swallowing during untrained tasks.

Due to the differences in outcomes between participants in the four-week pilot study and the two-week treatment study, further investigation into the effects of a longer period of skill training would be beneficial. As previously discussed, a four-week treatment protocol using the current methods was not feasible in this population. However, if a participant is able to complete the treatment task in their own home and at their own time then four weeks of daily treatment may not seem such a daunting task. Investigation of methods to improve adherence and engagement when completing the task at home would be beneficial to help facilitate longer treatment protocols. More research is required regarding the amount of therapist intervention that is necessary to ensure that participants not only complete the task correctly but are engaged whilst doing so.

Maintenance of swallowing function would be considered a beneficial outcome in this degenerative disease and many previous studies have reported reduced rate of decline as a measure of improvement. There was no significant deterioration observed in any of the outcome measures assessed. It is likely that the two-week period between assessments was not sufficient for significant disease progression and it cannot be concluded that the lack of deterioration was due to a maintenance effect. However, if treatment and/or monitoring had continued for a longer period of time, with a control group, then it is possible that a maintenance effect would have been observed in response to the skill training.

Although reliability was high for many of the outcome measures, there were some of concern. Measures of intra-rater reliability were good for UES opening distance and PCR; however, inter-rater reliability of these measures were poor. There was also a significant rater effect for both of these outcome measures, indicating a systematic difference between raters. For PCR and UES opening distance, the primary rater consistently rated lower than the

secondary rater. As there was a significant rater effect, it is likely that the raters differed in their interpretations of the instructions for measurement. Increasing the specificity of the instructions for completing the measurements may have increased the consistency of interpretation and therefore measurement reliability. Rater-effects were also demonstrated for CSA of the RAB, hyoid excursion measured with VFSS and US, supraglottic closure timing, airway closure timing and UES opening duration. Again, indicating the need for increased specificity of instructions for measurement. A significant effect of rating was also observed for measures of intra-rater reliability of timing aspects measured by VFSS. A rating effect indicates that these measurements were performed systematically differently the first time compared to the second time that they were measured. This could have an effect on the data as data that were extracted later may have been extracted differently to that which was performed earlier in the process. The order that data were extracted was random as a result of blinding, so systematic differences in analysis should not have led to falsely significant findings during data analysis.

Many of the hypotheses of this research hinged on the assumption that increased neuroplasticity as a result of swallowing skill training is possible in individuals with MND. Although there is evidence of increased neural activation during swallowing in the absence of functional swallowing changes (Li et al., 2009), more information is needed about the potential for neuroplasticity as a result of swallowing skill training. Neuroimaging that evaluates the areas of neural activation during swallowing before and after skill training at different stages of the disease process would help to inform us if and when neuroplasticity occurs in response to changes in environmental factors and the implementation of a treatment protocol.

11. Conclusion

For patients with MND, dysphagia is detrimental to quality and length of life. There is increasing evidence supporting the use of behavioural treatment to prolong function for individuals suffering from this degenerative disease. An important consideration when developing treatment options is optimising intensity to ensure patients benefit, whilst minimising the risk of adverse effects. Current guidelines suggest that exercises should be performed at a mild to moderate intensity to avoid fatigue, yet there are currently no clinically accessible means to identify fatigue of bulbar muscles. This research contributed to the literature by assessing one potential method of recognising fatigue. Measurement of submental sEMG amplitude during a lingual press task was not deemed a successful method, but potential explanations for this were identified. The limitations identified during this study will assist in developing future trials, as the ability to quantify fatigue in a clinically accessible manner remains an important objective.

Investigation of treatment options for relief from bulbar symptoms of MND has not progressed at the same rate as is observed in the limb literature. This research series investigated a novel approach to dysphagia treatment, focusing on training precision in movement patterns rather than muscle strength. This approach was investigated as an alternative to traditional strength training, due to the adverse effects that have been previously associated with muscle strengthening. The skill training protocol through the BiSSkiT software was well tolerated and easily followed by the individuals in this study, who varied in dysphagia severity and level of cognitive function. Importantly, there was no evidence of swallowing decline associated with the treatment or disease progression over the course of the protocol. Further, there was some evidence of improvement in quality of life and swallowing biomechanics following two weeks of treatment; however, these changes did not transfer to functional swallowing. Following four weeks of skill training during the pilot study, functional improvements were observed for the three patients with mild-moderate dysphagia, indicating potential transference as a result of a longer exposure to the protocol. This exploratory investigation did not reach a convincing conclusion regarding whether skill training with sEMG biofeedback is an effective treatment in this population. However, it highlighted potential positive outcomes that motivate further research and identified limitations of the current methodology that may guide future studies. Continued research investigating treatment options for improving or maintaining swallowing ability is necessary.

Due to the heterogeneity of the disease it is unlikely that there will be one treatment that is appropriate for all patients. Therefore, it is crucial to continue the investigation of novel treatment approaches that may be recommended to patients to reduce the significant burden associated with dysphagia.

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Appendices

Appendix A: Tables from study one results

Table A1. Median lingual press endurance time by trial

Trial	Median time (s)
1	34.6
2	26.6
3	15.8
4	18.4
5	16.5
6	15.8
7	11.4
8	13.9

Table A2. Post hoc comparisons of endurance time between sessions using Wilcoxon signed rank tests.

Trials compared	V	p-value
1-2	196	0.0802
2-3	210	0.02767
3-4	124	0.6869
4-5	145	0.8433
5-6	141	0.9406
6-7	187	0.1424
7-8	145	0.8462
1-8	255	0.0001066**

*Note: ** = significant at the .00625 level*

Table A3. Median sEMG amplitude for each trial

Trial	Median
1	18.29
2	25.23
3	23.35
4	26.5
5	27.88
6	27.79
7	26.88
8	34.73

Table A4. Post-hoc pair-wise comparisons of submental average sEMG amplitude

Trials compared	V	p-value
1-2	97	.2226
2-3	189	.1262
3-4	93	.1796
4-5	99	.2467
5-6	147	.7998
6-7	198	.06982
7-8	51	.006711*
1-8	57	.01229

*Note: * = approaching significance ** = significant at the .00625 level*

Appendix B: Tables from study three results

Table B1. Means and standard deviations of outcome measures over assessments

Measure	Bolus	Assessment 1 mean(sd)	Assessment 2 mean(sd)	Assessment 3 mean(sd)	Assessment 4 mean(sd)
TWST volume per swallow	N/A	12.2(6.51)	11.2(6.18)	11(7.1)	11.4(7.4)
TWST time per swallow	N/A	3.19(2.08)	3.34(2.07)	3.53(2.13)	3.47(1.97)
TWST volume per second	N/A	6.22(5.58)	5.21(4.74)	4.82(4.80)	5.27(5.36)
TOMASS bites	N/A	5.74(6.87)	5.42(5.27)	5(3.62)	5.24(3.38)
TOMASS chews	N/A	96.5(101)	91.2(76.4)	84.3(48.8)	83.8(53.8)
TOMASS swallows	N/A	5.37(5.57)	4.53(2.84)	4.74(2.88)	4.18(2.65)
TOMASS time	N/A	135(152)	117(78.9)	113(58.4)	105(60.8)
CSA of LAB	N/A	76.4(21.3)	71.5(13.3)	75.7(19.1)	71.8(17)
CSA of RAB	N/A	70.6(19.7)	73.8(12.4)	66.9(21.6)	65.7(13.6)
CSA of GH^+	N/A	182(36.1)	171(32.6)	165(49.1)	176(40.8)
Swal-QOL total	N/A	58.1(16.8)	53(18.6)	58.6(19.1)	59(19.4)
Swal-QOL oral	N/A	53.9(28.4)	55.3(23.4)	56.3(23.6)	59.4(26.9)
Swal-QOL pharyngeal	N/A	60.4(14.2)	54.9(17.2)	60(14.1)	57.6(18.6)
Swal-QOL secretions	N/A	47.4(26.6)	39.9(26.2)	42(31.3)	45.3(31.2)
Hyoid excursion (%) (US)	Dry	25(7.53)	22.1(10.2)	23.8(10.5)	25.6(8.63)
	Puree	25.1(8.95)	23.9(8.23)	24.9(8.94)	26.6(7.85)
	Water	26.6(9.12)	24.8(7.47)	24.9(8.67)	25.4(8.43)
Hyoid excursion (mm) (VFSS)	Cracker	21.6(4.27)	19.5(6.35)	18.1(8.19)	20.1(6.58)
	Puree	20.2(4.72)	16.9(6.45)	18.5(8.24)	21.4(7.55)
	Water	19.1(6.22)	18(6.09)	18.5(8.07)	20.9(8.39)
UES opening distance	Cracker	4.63(2.19)	5.16(1.93)	4.4(2.24)	4.86(2.11)
	Puree	4.64(1.89)	4.94(1.51)	5.21(1.83)	4.74(1.59
	Water	4.45(2.06)	4.67(1.33)	4.57(1.58)	4.65(1.36)

PCR	Cracker	0.09(0.06)	0.09(0.06)	0.08(0.04)	0.08(0.06)
	Puree	0.08(0.05)	0.07(0.06)	0.07(0.05)	0.09(0.05)
	Water	0.06(0.05)	0.07(0.06)	0.07(0.05)	0.06(0.05)
OPTT	Cracker	1.3(1.08)	1.32(1.27)	1.07(1.22)	1.15(1.78)
	Puree	0.702(0.53)	1.21(1.14)	1.17(1.06)	1.41(1.36)
	Water	0.582(0.76)	0.39(0.26)	0.74(0.88)	0.493(0.5)
HPTT	Cracker	0.474(0.13)	0.49(0.18)	0.44(0.1)	0.51(0.16)
	Puree	0.652(0.31)	0.61(0.18)	0.67(0.45)	0.6(0.15)
	Water	0.58(0.26)	0.54(0.24)	0.6(0.38)	0.58(0.27)
TPTT	Cracker	1.77(1.16)	1.81(1.38)	1.51(1.25)	1.66(1.83)
	Puree	1.36(0.72)	1.82(1.19)	1.83(1.13)	2.01(1.41)
	Water	1.15(0.83)	0.94(0.37)	1.35(0.95)	1.08(0.62)
Supraglottic closure	Cracker	0.03(0.12)	0.074(0.1)	0.024(0.081)	0.043(0.11)
timing	Puree	-0.001(0.12)	-0.011(0.082)	-0.037(0.068)	-0.018(0.10)
	Water	-0.13(0.115)	-0.11(0.12)	-0.11(0.11)	-0.12(0.12)
Airway closure	Cracker	0.81(0.25)	0.92(0.39)	0.81(0.3)	0.9(0.43)
duration	Puree	0.93(0.34)	0.96(0.6)	0.93(0.36)	1(0.67)
	Water	0.21(0.29)	0.84(0.28)	0.92(0.33)	0.9(0.49)
UES opening	Cracker	0.34(0.14)	0.34(0.1)	0.32(0.083)	0.38(0.15)
duration	Puree	0.45(0.11)	0.46(0.079)	0.45(0.066)	0.48(0.091
	Water	0.42(0.093)	0.43(0.11)	0.44(0.089)	0.44(0.095)

Table B2. Outcomes of likelihood ratio test

Measure	Bolus	Chi-sq (df)	p-value
TWST time per swallow	N/A	1.318 (3)	.725
TWST volume per swallow	N/A	2.35(3)	.503†
TWST volume per second	N/A	2.1(3)	.552†
TOMASS bites	N/A	1.71(3)	.635†
TOMASS masticatory cycles	N/A	0.56(3)	.906†
TOMASS swallows	N/A	1.23(3)	.746†
TOMASS time	N/A	0.33(3)	.953†
Swal-QOL total	N/A	7.94(3)	.047**
Swal-QOL pharyngeal	N/A	3.76(3)	.289

Swal-QOL oral	N/A	0.68(3)	.878
Swal-QOL secretions	N/A	2.83(3)	.418
CSA of GH^{+}	N/A	3.06(3)	.383
CSA of LAB	N/A	5.06(3)	.998†
CSA of RAB	N/A	.04(3)	.168†
Hyoid excursion (US)	Water	1.04(3)	.790
	Puree	0.66(3)	.882
	Dry	5.60(3)	.133
Hyoid excursion (VFSS)	Water	8.42(3)	.038 **
	Puree	21.0(3)	< .001 **
	Cracker	5.71(3)	.127
UES opening distance (VFSS)	Water	0.65(3)	.885
	Puree	4.89(3)	.18
	Cracker	4.66(3)	.200
Pharyngeal constriction ratio	Water	7.18(3)	.066 *
(VFSS)	Puree	3.45(3)	.327†
	Cracker	3.31(3)	.346
OPTT	Water	9.28(3)	.026 †**
	Puree	9.33(3)	.025† **
	Cracker	2.03(3)	.566†
HPTT	Water	3.06(3)	.383†
	Puree	.36(3)	.949†
	Cracker	6.03(3)	.11†
TPTT	Water	7.08(3)	.07† *
	Puree	7.04(3)	.071 †*
	Cracker	1.2(3)	.735†
Supraglottic closure timing	Water	1.0(3)	.800
	Puree	0.78(3)	.854†
	Cracker	1.18(3)	.754†
Airway closure duration	Water	2.69(3)	.441†
	Puree	0.27(3)	.965†
	Cracker	1.44(3)	.696†
UES opening duration	Water	0.65(3)	.885

	Puree	5.09(3)	.165
	Cracker	5.94(3)	.114†

Note: †= did not meet assumptions - non-parametric statistics used, * = p-value is significant at the .1 level, ** = p-value is significant at the .05 level

Table B3. Outcomes from post-hoc analyses investigating between assessment differences of measures with a significant effect of assessment session

Measure	Assessments compared	Outcome
Swal-QOL total	2-1	-4.31 (95% CI [-10.23, 1.62], p = .068) *
	3-2	5.59 (95% CI [-0.22, 11.4], p = .017) **
	4-3	-0.05 (95%CI [-5.96, 5.85], p = .982)
Pharyngeal constriction ratio (water)	2-1	0.007 (95% CI [-0.01, 0.02], p = .297)
	3-2	-0.007 (95% CI [-0.02, 0.01], p = .3)
	4-3	-0.01 (95% CI [-0.03, 0.006], p = .103)
Hyoid displacement (water)	2-1	-1.18 (95% CI [-4.1,1.73], p = .301)
	3-2	.82 (95% CI [-2.12, 3.76], p = .476)
	4-3	2.4 (95% CI [-0.56, 5.36], p = .04)**
Hyoid displacement (puree)	2-1	-3.34 (95% CI [-5.97, -.71], p = .001) **
	3-2	1.69 (95% CI [-0.93, 4.32], p = .1)
	4-3	2.84 (95% CI [.26, 5.43], p = .006) **

Note: * = p-value is significant at the .1 level, ** = p-value is significant at the .05 level

Table B4. Outcome of Friedman's tests for data that did not meet the assumptions required for parametric testing.

Measure	Bolus	Chi-sq (df)	p-value
TWST volume per swallow	N/A	2.35(3)	.503†
TWST volume per second	N/A	2.1(3)	.552†
TOMASS bites	N/A	1.71(3)	.635†
TOMASS masticatory cycles	N/A	0.56(3)	.906†

TOMASS swallows	N/A	1.23(3)	.746†
TOMASS time	N/A	0.33(3)	.953
CSA of LAB	N/A	5.06(3)	.998†
CSA of RAB	N/A	.04(3)	.168†
PCR	Puree	3.45(3)	.327†
OPTT	Water	9.28(3)	.026 †**
	Puree	9.33(3)	.025† **
	Cracker	2.03(3)	.566†
HPTT	Water	3.06(3)	.383†
	Puree	.36(3)	.949†
	Cracker	6.03(3)	.11†
TPTT	Water	7.08(3)	.07† *
	Puree	7.04(3)	.071 †*
	Cracker	1.2(3)	.735†
SGCT	Puree	0.78(3)	.854†
	Cracker	1.18(3)	.754†
ACD	Water	2.69(3)	.441†
	Puree	0.27(3)	.965†
	Cracker	1.44(3)	.696†
UES opening duration	Cracker	5.94(3)	.114†

Note: * = p-value is significant at the .1 level, ** = p-value is significant at the .05 level

Table B5. Median scores by assessment session of outcome measures with significant effect of assessment session.

Outcome measure	Assessment	Median
OPTT (water)	Baseline	0.36
	Pre-tx	0.315
	Post-tx	0.37
	Follow-up	0.385
OPTT (puree)	Baseline	0.58
	Pre-tx	1.03
	Post-tx	0.9
	Follow-up	1.045

TPTT (water)	Baseline	0.885
	Pre-tx	0.845
	Post-tx	0.965
	Follow-up	0.875
TPTT (puree)	Baseline	1.345
	Pre-tx	1.76
	Post-tx	1.53
	Follow-up	1.8

Table B6. Post-hoc analyses investigating outcome measures with a significant effect of assessment session:

Measure	Assessment	V	p-value
OPTT (water)	2-1	38.5	.657
OPTT (water)	3-2	7	.019 **
OPTT (water)	4-3	55	.054 *
OPTT (puree)	2-1	58	.024 **
OPTT (puree)	3-2	61	.01 **
OPTT (puree)	4-3	61	.01 **
TPTT (water)	2-1	37	.765
TPTT (water)	3-2	6	.0184 **
TPTT (water)	4-3	40	.044 **
TPTT (puree)	2-1	59	.019 **
TPTT (puree)	3-2	64	.003 **
TPTT (puree)	4-3	60	.014 **

Note: * = p-value is significant at the .1 level, ** = p-value is significant at the .05 level

Table B7. Outcome of Friedman's tests investigating a difference in the amount of change in outcome measures over the baseline, treatment and follow-up periods.

Measure	Bolus	Chi-sq (df)	p-value
TWST volume per swallow	N/A	0.585 (2)	0.747
TWST time per swallow	N/A	0.875 (2)	0.646
TWST volume per second		1.125 (2)	0.57

TOMASS bites	N/A	0.037 (2)	0.982
TOMASS masticatory cycles	N/A	0.394 (2)	0.821
TOMASS swallows	N/A	0.375 (2)	0.829
TOMASS time	N/A	0.118 (2)	0.943
CSA of LAB	N/A	0.133 (2)	0.936
CSA of RAB	N/A	3.857 (2)	.145
CSA of GH^{+}	N/A	1.412 (2)	.494
Swal-QOL total	N/A	7.125 (2)	.028 **
Swal-QOL oral	N/A	0.613 (2)	.736
Swal-QOL pharyngeal	N/A	1.58 (2)	.454
Swal-QOL secretions	N/A	0.47 (2)	.47
UES opening distance	Water	0.727 (2)	.695
	Puree	1.273(2)	.529
	Cracker	0.727 (2)	.695
Pharyngeal Constriction Ratio	Water	0.326 (2)	.85
	Puree	1.256 (2)	.534
	Cracker	5 (2)	.082*
Hyoid Excursion(VFSS)	Water	2.909 (2)	.234
	Puree	5.091 (2)	.078*
	Cracker	4.222 (2)	.121
OPTT	Water	8.909 (2)	.012 **
	Puree	7.818 (2)	.02 **
	Cracker	3.2 (2)	.202
HPTT	Water	1.273 (2)	.529
	Puree	0.727 (2)	.695
	Cracker	4.546 (2)	.103
TPTT	Water	5.628 (2)	.06*
	Puree	5.091 (2)	.078*
	Cracker	1.4 (2)	.497
SGCT	Water	0.545 (2)	.761
	Puree	0.545 (2)	.761
	Cracker	3.436 (2)	.179

ACD	Water	0.182 (2)	.913
	Puree	1.273 (2)	.529
	Cracker	2.6 (2)	.273
UES opening duration	Water	0.182 (2)	.913
	Puree	1.636 (2)	.441
	Cracker	3.818 (2)	.148

Note: * = p-value is significant at the .1 level, ** = p-value is significant at the .05 level

Table B8. Post-hoc comparisons of the outcome measures that were identified as significant

Measure	Periods compared	V	p-value
Swal-QOL total	Baseline - treatment	29	.023 **
	Treatment – follow-up	111	.107
	Baseline-follow-up	43	.205
PCR(cracker)	Baseline - treatment	39	.275
	Treatment – follow-up	11	.106
	Baseline-follow-up	21	.557
Hyoid excursion (puree, VFSS)	Baseline - treatment	17	.175
	Treatment – follow-up	27	.638
	Baseline-follow-up	6	.014**
OPTT (water)	Baseline - treatment	10	.042**
	Treatment – follow-up	61	.01**
	Baseline-follow-up	38	.7
OPTT(puree)	Baseline - treatment	51	.123
	Treatment – follow-up	21	.32
	Baseline-follow-up	51	.123
TPTT (water)	Baseline - treatment	17	.175
	Treatment – follow-up	52	.014**

	Baseline-follow-up	55	.054*
TPTT(puree)	Baseline - treatment	46	.278
	Treatment – follow-up	54	.067*
	Baseline-follow-up	28	.7

Note: * = p-value is significant at the .1 level, ** = p-value is significant at the .05 level

Table B9. Median amount of change over baseline, treatment and follow-up periods of the outcome measures with significant difference between periods.

Outcome measure	Period	Median
Swal-QOL total	Baseline	-3.57
	Treatment	5.36
	Follow-up	0
PCR(cracker)	Baseline	0.00436
	Treatment	-0.0186
	Follow-up	0.00677
Hyoid excursion	Baseline	-5.73
(puree, VFSS)	Treatment	0.51
	Follow-up	2.5
OPTT (water)	Baseline	-2.08
	Treatment	-0.147
	Follow-up	-2.02
OPTT(puree)	Baseline	0.39
	Treatment	-0.203
	Follow-up	0.103
TPTT (water)	Baseline	0.0233
	Treatment	0.167
	Follow-up	-0.14
TPTT(puree)	Baseline	0.353
	Treatment	-0.13
	Follow-up	-0.0367

Appendix C: Information sheets and consent forms

INFORMATION SHEET

Department of Communication Disorders

Telephone: +64 3 369 2385

Email: paige.thomas@pg.canterbury.ac.nz

19 May 2016

Strength and endurance of submental and lingual muscles in healthy individuals

I am a PhD student in the Department of Communication Disorders performing a research project in conjunction with two students from Lincoln High School. You are invited to take part in a study investigating the effects of fatigue on the strength and endurance of muscles in your tongue. Results from this study will help us to design effective assessment and treatment for people with swallowing disorders.

You can join this study if you are 20 years or older, have no medical problems that may affect your swallowing and are clean shaven under your chin (to allow the sensors to detect muscle activity). Your involvement in this project will be to attend one session in which you will be asked to press a soft plastic sensor between your tongue and the roof of your mouth and hold it there as hard as you can for 45 seconds. This sensor will measure how much force you can apply with your tongue. There will also be a small adhesive patch placed under your chin which contains sensors that will measure the activity of muscles as you perform the task. This task will be repeated 10 times with small breaks between trials. This will help us determine when and how much the muscle of the tongue get tired over time. The electrodes and tongue bulb can be easily removed at the completion of the study. The session will take approximately 30 minutes including the set-up of equipment.

Information about your tongue strength and endurance will be stored on the computer as a waveform and analysed at another time. The only data recorded will be the lines that represent your tongue strength and muscle activity. To ensure anonymity and confidentiality, no material which could personally identify you will be used on the computer that stores the data, or in any reports. All hard-copy information will be kept in a locked filing cabinet which will be kept at the Rose Centre for Stroke Recovery and Research or stored on a password protected computer. The only people that will have access to the data are the

researcher, the research assistants from Lincoln High School and the supervisor. Data will be kept for a period of 10 years following which time it will be destroyed.

Unfortunately due to the limited funding for this project we cannot offer you any further token of appreciation for participation. The only benefit to you is that your participation gives important information about swallowing in healthy adults. There are no known risks of using small sensors to monitor muscle activity. Participation is voluntary and you are free to withdraw at any time, without having to give a reason. This will in no way affect any future care or treatment, or academic participation if you are a student. However, as there will be no identifying information stored alongside your data, following completion of the session it will become difficult to identify and remove your data from the study. You will be offered copies of the final manuscript of this project or a basic summary. However, you should be aware that a significant delay may occur between completion of data collection and the final report. Alternatively, or in addition, you can choose to have the results of the study discussed with you personally by the principal investigator.

Results from this project may be included in the researcher's PhD thesis and may be submitted for publication in a peer-reviewed journal. A thesis is a public document and will be available through the UC Library. Please use the consent form to indicate to the researcher if you would like to receive a copy of the final manuscript or a basic summary of the results. However, please be aware that there may be a long delay between data collection and completing the final report.

I am carrying out this project as a requirement of a doctoral degree under the supervision of Professor Maggie-Lee Huckabee. You can contact the principal investigator if you require any further information about the study during work hours at (03) 364 2307 or via email: paige.thomas@pg.canterbury.ac.nz. Prof Huckabee can be contacted at maggie-lee.huckabee@canterbury.ac.nz.

This project has been reviewed and approved by the University of Canterbury Human Ethics Committee, and participants should address any complaints to The Chair, Human Ethics Committee, University of Canterbury, Private Bag 4800, Christchurch (human-ethics@canterbury.ac.nz).

If you agree to participate in the study, you are asked to complete the consent form and return to the researcher.

Paige Thomas
Department of Communication Disorders

Telephone: + 64 3 369 2385

Email: paige.thomas@pg.canterbury.ac.nz

CONSENT FORM

Department of Communication Disorders
Telephone: +64 3 364 2307
Email: paige.thomas@pg.canterbury.ac.nz
19 May 2016

Strength and endurance of submental and lingual muscles in healthy individuals

I have been given a full explanation of this project and have had the opportunity to ask questions. I understand what will be required of me if I agree to take part in this research. I understand that my participation is voluntary and that I may withdraw at any stage without penalty. Withdrawal of participation will also include the withdrawal of any information I have provided should this remain practically achievable.

I understand that any information or opinions I provide will be kept confidential to the researchers and two Lincoln High School Students and that any published or reported results will not identify me. I understand that all data collected for this study will be kept in locked and secure facilities or on password protected electronic form at the Rose Centre for Stroke Recovery & Research and will be destroyed after ten years.

I understand the risks associated with taking part and how they will be managed. I understand that I am able to receive a report on the findings of the study at the conclusion of the project by checking the box below. I understand that if I require further information I can contact the researcher, Paige Thomas (paige.thomas@pg.canterbury.ac.nz) for further information, or her supervisor Professor Maggie-Lee Huckabee (maggie-lee.huckabee@canterbury.ac.nz). If I have any complaints about the research, I can contact the University of Canterbury Human Ethics Committee Private Bag 4800, Christchurch (human-ethics@canterbury.ac.nz).

☐ I would like to receive a summary of the results of the project.

Email: _____

By signing below, I agree to participate in this research project.

Date _____

Print Name of Participant _____

Signature of Participant _____

Please return this consent form to Paige Thomas (paige.thomas@pg.canterbury.ac.nz

Information Sheet for Participants

Department of Communication Disorders

The Rose Centre for Stroke Recovery and Research

+64 3 364 2042

maggie-lee.huckabee@canterbury.ac.nz

07 January 2016

An exploratory study of skill-based swallowing training in patients with motor neurone disease.

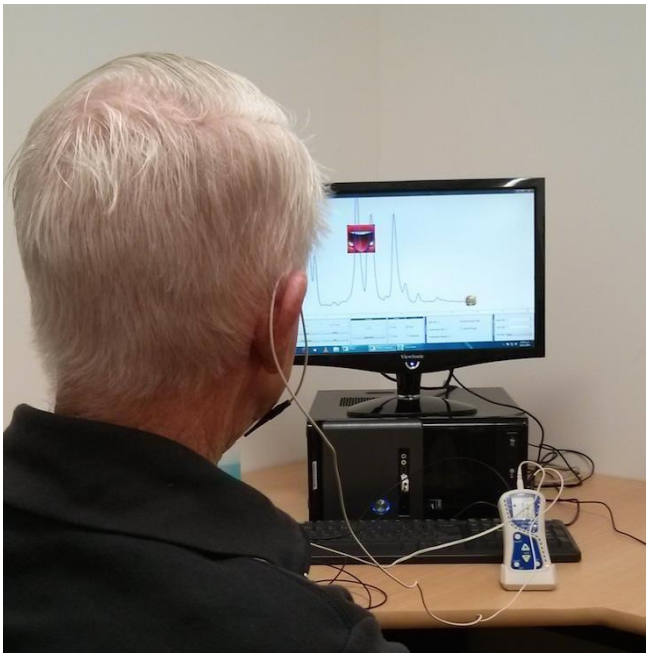
I am a Professor in the Department of Communication Disorders and Director of the Rose Centre for Stroke Recovery and Research and am leading this project in conjunction with clinical director Sara Moore, PhD student Paige Thomas and honours student Michelle Westley. The purpose of this research is to evaluate if a novel skill-based swallowing therapy has the potential to improve health and quality of life in patients with motor neurone disease.

This first study will help us decide if we should proceed to a larger clinical trial.

If you choose to take part in this study, your involvement in this project will be commitment to four evaluation sessions and 20 treatments sessions across three months. During the evaluation sessions, you will complete two questionnaires about your swallowing, will be asked to drink water and eat a dry cracker and will have the muscles under your chin measured during swallowing with a non-invasive test called ultrasound. Evaluation sessions will require video recording, however we will shield your upper face and eyes to reduce potential for recognition. These tasks will be completed during all four assessment sessions.

The treatment sessions will involve placing a small adhesive disc containing electrodes on the underside of your chin to measure electrical activity from your muscles during swallowing. You will be instructed to swallow and will view a feedback graph on the computer screen that

shows you when and how hard you swallow. Your task is to swallow so that the peak of the waveform falls in a target on the screen. See the figure below.



Each treatment session will last approximately one hour in duration including rest periods, plus an additional 5 or 10 minutes of set-up time. Treatment sessions will be completed every work day for one month. At least 10 of these sessions must be completed with the researcher; however there may be an option of doing some of the treatment sessions individually if you have an appropriate computer to run the software.

The only identified risk associated with this research is the possibility that you may get food or fluid in your lungs when you eat or drink the cracker for assessment. The researchers conducting the study and supervising the student have clinical backgrounds in managing swallowing disorders and recognising signs and symptoms of aspiration. We can and will adapt data collection to minimise risk if we feel that you are not safe in your swallowing. We understand that a diagnosis of motor neurone disease can be quite upsetting to you and your family. We encourage you to involve your family/whanau or other people who support you in any or all session appointments. With consent, referrals to the Motor Neuron Disease Association can be made for additional support for you if you are not already involved with this organisation.

Participation is voluntary and you have the right to withdraw at any stage without penalty. You may ask for your raw data to be returned to you or destroyed at any point. If you withdraw, we will remove information relating to you.

The results of the project may be published, but you can be assured of the complete confidentiality of data gathered in this investigation: your identity will not be made public. To ensure anonymity and confidentiality, documentation will be recorded using participant numbers and will be kept in locked filing cabinets for the duration of the study. Data from questionnaires will be coded using participant numbers and original copies will be shredded.

Hard copies and digital data will be stored for a period of ten years at the University of Canterbury Rose Centre for Stroke Recovery and Research, at which time they will be destroyed by the primary researcher. Please indicate to the researcher on the consent form if you would like to receive a copy of the summary of results of the project.

This project has been reviewed and approved by the University of Canterbury Human Ethics Committee, and participants should address any complaints to The Chair, Human Ethics Committee, University of Canterbury, Private Bag 4800, Christchurch (humanethics@canterbury.ac.nz).

If you agree to participate in the study, you are asked to complete the consent form and return this to one of the researchers.

Information Sheet for Participants

Department of Communication Disorders
The Rose Centre for Stroke Recovery and Research
+64 3 364 2042
maggie-lee.huckabee@canterbury.ac.nz
07 January 2016

An exploratory study of skill-based swallowing training

in patients with motor neurone disease.

☐ I have been given a full explanation of this project and have had the opportunity to ask questions.

☐ I understand what is required of me if I agree to take part in the research.

☐ I understand that participation is voluntary and I may withdraw at any time without penalty. Withdrawal of participation will also include the withdrawal of any information I have provided should this remain practically achievable.

☐ I understand that any information or opinions I provide will be kept confidential to the researcher and supervisor and that any published or reported results will not identify the participants.

☐ I understand that all data collected for the study will be kept in locked and secure facilities and/or in password protected electronic form and will be destroyed after ten years.

☐ I understand the risks associated with taking part and how they will be managed.

☐ I understand that I am able to receive a report on the findings of the study by contacting the researcher at the conclusion of the project.

☐ I understand that I can contact the primary researcher Maggie-Lee Huckabee (maggielee.huckabee@canterbury.ac.nz), Paige Thomas (paige.thomas@pg.canterbury.ac.nz) or Sara Moore (sara.moore@canterbury.ac.nz) for further information. If I have any complaints, I can contact the Chair of the University of Canterbury Human Ethics Committee, Private Bag 4800, Christchurch (human-ethics@canterbury.ac.nz)

☐ I would like a summary of the results of the project.

☐ By signing below, I agree to participate in this research project.

Name:_____Signed_____Date_____

Email (for report of findings if applicable:_____

Please return this form to one of the researchers listed above.

PARTICIPANT INFORMATION SHEET

Department of Communication Disorders
Email: paige.thomas@pg.canterbury.ac.nz, emma.burnip@pg.canterbury.ac.nz
6th December 2017

Study title: **Skill-based swallowing training for patients with Motor Neurone Disease**
Lead investigators: Paige Thomas and Emma Burnip
Contact phone number: 03 369 2385 Locality: Canterbury
Ethics Committee ref: 17/NTB/214

You are invited to take part in a study on an intervention for swallowing difficulties in Motor Neurone Disease (MND). Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason, and it won't affect the care you receive. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you'd like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.
If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 6 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

- I am Paige Thomas, a Speech-Language Therapist and PhD student. With a fellow PhD student, Emma Burnip, we are researching a skill-based swallowing therapy.
- At the moment, there are no options to treat people with swallowing problems caused by MND.
- We want to find out whether this new intervention can help swallowing and quality of life in people with MND.
- This intervention uses ideas of skill training and biofeedback to see if people with MND can control their own swallowing when they can visualise it on a screen.
- All volunteers will receive the intervention. We will compare measures of swallowing before and after therapy to see if there are any changes.

- This study is being funded by the University of Canterbury Rose Centre for Stroke Recovery and Research as part of our PhD projects.
- This study has been approved by Northern B HDEC.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

- You can join this study if you are 18 years or older and have been diagnosed with the Amyotrophic Lateral Sclerosis type of MND. You must have noticed some changes in how you are swallowing but still be eating and drinking.
- You cannot take part if you have another condition that affects your swallowing, if you are pregnant, or if you have had a facial trauma.
- If you choose to take part in this research, you will complete 4 assessment sessions and 10 intervention sessions over 6 weeks.
- If you sign the consent form, there will be a short questionnaire about swallowing to ensure that you can take part in this study. We will also request general information such as your age, weight, height and stage of MND. You will be asked to do a short assessment of thinking skills, this will be recorded once as part of the general information before we start the study.

In assessment sessions you will:

- Fill in a questionnaire about your swallowing.
- Eat a cracker and drink some water.
- Have the muscles under your chin measured with an ultrasound device when you swallow. Ultrasound is a safe procedure which uses high frequency sound waves (like those that a bat uses to navigate dark caves) to produce an image of your swallowing muscles.

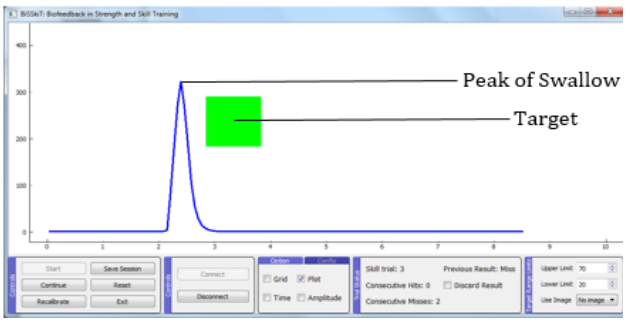
If you are able to travel to the clinic you may also:

- Have the pressures in your throat measured when you swallow - a small catheter the size of a piece of spaghetti will be inserted into your nose which you will swallow down.
- Have an x-ray study of your swallowing.

One part of the assessment session will need to be video-taped. This video will only be used by the researcher to analyse your chewing and swallowing.

In the intervention sessions:

- A small sticky patch will be placed over the muscles under your chin. This patch will be used to measure the activity of your muscles when you swallow. Your swallowing muscle activity will be displayed on a computer screen (see image). There will be a target box on the screen, your task will be to swallow so that the peak of the line lands in this box.



- Each intervention session will last one hour including rest periods.
- Intervention sessions will be five days per week for two weeks.
- If you are in Christchurch and able to travel, intervention and assessment sessions will be carried out at the UC Rose Centre located in at St George's Medical Centre.

- If you are not in Christchurch or are unable to travel to the Rose Centre, intervention sessions and aspects of the assessment may be completed in your home

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

- There are no known risks of this intervention, but, there are risks that you should be aware of in the assessment sessions. The researchers with you during the study are trained Speech Therapists and are able to manage these risks.
- There is a slight risk that during assessment you may get food or fluid in your lungs, however, the risk here is no more than when you eat and drink at home.
- The x-ray of your swallowing will involve exposure to radiation. The level of radiation required for this assessment is very low (it is about half of the radiation exposure you would have on a long haul flight) and is not likely to cause any negative effects. Please inform the researcher if you think you may be pregnant, as this radiation exposure is not recommended for the developing baby.
- You may find that placement of the catheter to measure throat pressures is uncomfortable. There is a small risk of a nose bleed or fainting during this assessment. We will work with you to ensure that you are comfortable during assessments and alter them if needed.
- We encourage you to involve your family or support network in any/all appointments.
- These assessments will give us very detailed measurements of your swallowing. This means we can detect any changes as a result of the intervention.

WHO PAYS FOR THE STUDY?

- For participating in this research, we will offer you petrol vouchers to cover travel costs (based on the IRD Mileage Rate of $0.73 per km).
- You do not need to pay any other costs to take part in this study.
- The study is funded by the University of Canterbury Rose Centre for Stroke Recovery and Research as part of my PhD project. We have applied for a project grant from the Neurological Foundation of New Zealand. We are expecting to hear the outcome of this application in December 2018.

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study, which is unlikely, you would be eligible to apply for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery. If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.
If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT ARE MY RIGHTS?

- Whether or not you take part is your choice. If you do not want to take part, you do not have to give a reason. This will not affect your future care or intervention.

- You will be told of any new information about adverse or beneficial effects related to the study that becomes available during the study that may have an impact on your health.
- If you find the intervention helpful, there may be an option to access the intervention at home after the study. This is dependent on the equipment that is available at that time. Please talk to the researcher at any time if you would like to discuss this option.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

- Nothing that could identify you will be stored with your results. All hard-copy data will be kept in a locked filing cabinet at the Rose Centre for Stroke Recovery and Research or stored on a password protected computer. The only people who will have access to the data are the researchers and their supervisor. Data will be kept for 10 years following which time it will be destroyed.
- Results from this project will be included in my PhD thesis and may be published in a peer-reviewed journal. A thesis is public and will be available through the UC Library, but your identity will not be made public.
- If you do want to take part now, but change your mind later, you can pull out of the study at any time.
- You may ask for your data to be returned to you or destroyed at any time up to the point when analysis of raw data begins.
- Please use the consent form to indicate if you would like to receive a summary of the results. Please be aware that there may be a delay between data collection and completing the final report in early 2020.
- If you agree to participate in the study, you are asked to complete the consent form and return to the researcher.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact:
Name: Paige Thomas or Emma Burnip, PhD Candidates,
Department of Communication Disorders, University of Canterbury
Telephone number: 03 369 2385
Email: emma.burnip@pg.canterbury.ac.nz, paige.thomas@pg.canterbury.ac.nz
Name: Professor Maggie-Lee Huckabee, PhD Supervisor,
Department of Communication Disorders, University of Canterbury
Telephone number: 03 369 5124 Email: maggie-lee.huckabee@canterbury.ac.nz.

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on: Phone: 0800 555 050
Fax: 0800 2 SUPPORT (0800 2787 7678) Email: advocacy@hdc.org.nz
For Maori Heath support please contact :
Name: Catherine Grant, Administrator for He Kamaka Waiora (Māori Health Team)
Telephone number: 09 486 8324 ext 2324 Email: catherine.grant@cdhb.health.nz

You can also contact the health and disability ethics committee (HDEC) that approved this study on: Phone: 0800 4 ETHICS Email: hdecs@moh.govt.nz

CONSENT FORM

Department of Communication Disorders
Telephone: +64 3 369 2385
Email: paige.thomas@pg.canterbury.ac.nz
6th December 2017

Skill-based swallowing training for patients with Motor Neurone Disease
If you need an INTERPRETER, please tell us.

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.
I have been given sufficient time to consider whether or not to participate in this study.
I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.
I consent to the research staff collecting and processing my information, including information about my health.
If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.
I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study.
I understand that there may be risks associated with the assessment in the event of myself becoming pregnant. I take responsibility to inform the investigator if there is any chance that I may be pregnant whilst taking part in the study.

I agree to an approved auditor appointed by the New Zealand Health and Disability Ethic Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.	
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.	
I understand the compensation provisions in case of injury during the study.	
I know who to contact if I have any questions about the study in general.	
I understand my responsibilities as a study participant.	

I wish to receive a summary of the results from the study. Yes ☐ No ☐

If yes to the above- email: _____

Declaration by participant:

I hereby consent to take part in this study.

Participant's name: _____

Signature: _____ Date: _____

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name: _____

Signature: _____ Date: _____

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INFORMED CONSENT

Protocol Title: Skill-based dysphagia therapy as an intervention for individuals with Neurodegenerative disease.

Principal Investigators:

Paige Thomas, MSLP: 212-678-3072; pat2151@tc.columbia.edu

Dr. Michelle S. Troche, PhD/CCC-SLP: 212-678-3072; UADLAB@tc.columbia.edu

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INTRODUCTION

You are invited to participate in research to test if skill-based swallowing therapy has the potential to improve swallowing and quality of life in patients with neurodegenerative disease. You may qualify to participate in this study because you have a diagnosis of Amyotrophic Lateral Sclerosis (ALS) OR Huntington's Disease (HD). Approximately 24 people will participate in this study. The therapy portion of this research will run over two weeks with five one-hour sessions per week. Additionally, there will be a total of four assessment sessions to monitor your swallowing changes, each of these assessment sessions will take approximately 40 minutes.

To be included in this study you must be over 18 years of age and have a diagnosis of ALS or over 30 years of age and have a diagnosis of HD. You must have noticed some changes to your swallowing as a result of ALS or HD, these may be minor. Despite these changes, oral intake must continue to be your main source of nutrition. You will be excluded from study participation if you have another condition that may affect your swallowing.

Audio and video recording is part of this study. **If you do not wish to be audio/video-recorded, you will not be able to participate.**

WHY IS THIS STUDY BEING DONE?

Swallowing impairments are common in people with ALS and HD. However, there is currently no therapy which is commonly used to slow swallowing decline. We know very little about swallowing therapy for those with ALS or HD and this study will increase knowledge about the effects of therapy.

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WHAT WILL I BE ASKED TO DO IF I AGREE TO TAKE PART IN THIS STUDY?

First, we will need to make sure you are eligible for study participation. We will briefly test your cognition and your opinion of your swallowing ability.

If we find that you are able to participate, you will need to come to our research labs at Teachers College Columbia University for a total of 13 visits. This will consist of 9 treatment sessions, 3 assessment sessions and one session in which both assessment and treatment can be done on the same day.

At each of these visits, you will be working with either the principal investigator or one of the research staff. If you choose to participate, you will be asked to participate in the following tasks:

Assessment visits (Approximately 30 minutes).

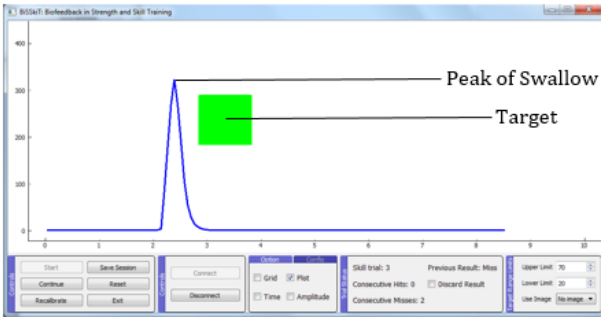
In each assessment session you will:

1. Fill in a questionnaire about your swallowing and how this effects your quality of life.
2. Fill in a questionnaire about your functional ability.
3. Eat a saltine cracker as quickly as you can do so comfortably.
4. Drink a glass of water as quickly as you can do so comfortably.
5. Have the muscles under your chin measured both while sitting still and while swallowing using ultrasound. This is a non-invasive assessment that uses high frequency sound waves to produce an image of muscles and various other structures which are important for swallowing.

As previously mentioned, portions of this assessment will require video recording. We will try to record only from your nose down as this will help to reduce the potential for recognition.

Therapy visits (Approximately 1 hour).

Therapy will take place at the Upper Airway Dysfunction Lab five days per week for two weeks. The treatment sessions will use skill training and aim to improve the precision of your swallowing. This will involve placing a small self-adhesive patch which contains electrodes (surface electromyography) on the underside of your chin. This patch will be used to measure and display the activity of your swallowing muscles as a waveform on the computer screen. There will also be a box displayed on the screen, your task will be to swallow so that the peak of the waveform falls within this target box. Each treatment session will last approximately one hour including rest periods.



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There will be a total of four assessment and ten therapy sessions over the course of six weeks. Assessments will be every two weeks with therapy for the two weeks between assessment two and assessment three. The four assessment sessions allows us to monitor natural changes to your swallowing when you are not receiving therapy, any changes as a result of the therapy, and to assess whether any effects seen as a result of therapy continue after therapy finishes.

WHAT POSSIBLE RISKS OR DISCOMFORTS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

This is a minimal risk study, which means the harms or discomforts that you may experience are not greater than you would ordinarily encounter in daily life while taking routine physical or psychological examinations or tests. You will be eating and drinking foods and liquids of different consistencies. As you have swallowing difficulties, there is the risk of food or liquid going into your lungs during assessment. However, this risk is no more than when you are eating or drinking at home. If there is evidence of food or fluid going into your lungs we will stop testing immediately. As some of the sessions are long it is possible that they will make you feel tired. If you start to feel tired you will have an opportunity to rest prior to continuing with further treatment or assessment.

There are no known risks associated with the therapy task. You will be given breaks throughout the therapy sessions and offered sips of water during these breaks.

The investigators and research staff are taking precautions to keep your information confidential and prevent anyone from discovering or guessing your identity, such as using a randomized ID number instead of your name next to all data and keeping all information on a password protected computer or locked in a file drawer at Teachers College.

WHAT POSSIBLE BENEFITS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

There are not direct benefits associated with taking part in this research. In a previous study, skill training for swallowing had beneficial effects on swallowing outcomes for individuals with Parkinson's disease, another neurodegenerative disease. However, the effects of this therapy for individuals with ALS or HD are currently unknown.

WILL I BE PAID FOR BEING IN THIS STUDY?

You will not be paid to participate; however, we will give you a $75 Walgreens voucher to thank you for volunteering. There are no costs to you for taking part in this study.

WHEN IS THE STUDY OVER? CAN I LEAVE THE STUDY BEFORE IT ENDS?

The study is over when you have completed the final assessment session. However, you can leave the study at any time even if you haven't finished.

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PROTECTION OF YOUR CONFIDENTIALITY

The investigators will keep all written materials locked in a desk drawer in a locked office. Any electronic or digital information (including video and audio recordings) will be stored on a computer that is password protected. A master list matching your identifying information with your assigned de-identified code will be kept in a locked and separated from the documents with your de-identified code and visit (non-identifying) data. As part of our practice, we will hold onto all de-identified data for 10 years before securely discarding.

HOW WILL THE RESULTS BE USED?

Results from this research will be included in the researcher's PhD thesis and may be submitted for publication in a peer-reviewed journal or as a presentation at a conference. Your name or any identifying information about you will not be published. A thesis is a public document and will be available online, but you can be assured that you identity will not be made public.

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CONSENT FOR VIDEO RECORDING

Video recording is part of this research study. You can choose whether to give permission to be recorded. If you decide that you do not wish to be recorded, you will not be able to participate in this research study.

_____I give my consent to be video recorded_____

Signature

_____I **do not** consent to be audio/video recorded_____

Signature

WHO MAY VIEW MY PARTICIPATION IN THIS STUDY

___I consent to allow written, video and/or audio taped materials viewed at an educational setting or at a conference outside of Teachers College_____

Signature

___I **do not** consent to allow written, video and/or audio taped materials viewed outside of Teachers College Columbia University_____

Signature

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OPTIONAL CONSENT FOR FUTURE CONTACT

The investigator may wish to contact you in the future. Please initial the appropriate statements to indicate whether or not you give permission for future contact.

I give permission to be contacted in the future for research purposes:

Yes _____ No_____
Initial Initial

I give permission to be contacted in the future for information relating to this study:

Yes _____ No_____
Initial Initial

WHO CAN ANSWER MY QUESTIONS ABOUT THIS STUDY?

If you have any questions about taking part in this research study, you should contact the principal investigator, Paige Thomas, at 212-678-3072 or at pat2151@tc.columbia.edu You can also contact her academic supervisor, Dr. Troche at 212-678-3953 or at mst2139@tc.columbia.edu

If you have questions or concerns about your rights as a research subject, you should contact the Institutional Review Board (IRB) (the human research ethics committee) at 212-678-4105 or email IRB@tc.edu. Or you can write to the IRB at Teachers College, Columbia University, 525 W. 120th Street, New York, NY 1002. The IRB is the committee that oversees human research protection for Teachers College, Columbia University.

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INFORMED CONSENT

PARTICIPANT'S RIGHTS

- I have read and discussed the informed consent with the researcher. I have had ample opportunity to ask questions about the purposes, procedures, risks and benefits regarding this research study.
- I understand that my participation is voluntary. I may refuse to participate or withdraw participation at any time without penalty.
- The researcher may withdraw me from the research at his or her professional discretion.
- If, during the course of the study, significant new information that has been developed becomes available which may relate to my willingness to continue my participation, the investigator will provide this information to me.
- Any information derived from the research study that personally identifies me will not be voluntarily released or disclosed without my separate consent, except as specifically required by law.
- I should receive a copy of the Informed Consent document.

My signature means that I agree to participate in this study

Print name: _____ **Date**: _____

Signature: _____

ID #_____

HIPAA RESEARCH AUTHORIZATION

Authorization for the Creation, Use, and Disclosure of Protected Health Information for Institutional Review Board Approved Research

Instructions: This authorization should be attached to each Informed Consent Form.
Investigators: Please complete information fields below and questions 2-8. Leave the name of research subject and signature areas blank.

Title of Study: **Skill-based dysphagia therapy as an intervention for individuals with Neurodegenerative disease.**
Name of Principal Investigator: *Paige Thomas, MSLP*
Phone Number: *212-678-3072* Sponsor:
IRB Protocol Number: _____ Protocol Approval Date:

This form authorizes **Teachers College, Columbia University (TC)** to use and disclose certain protected health information about _____(Name of research subject) that we will collect and create in this research study.

This authorization is voluntary, and you may refuse to sign this authorization. If you refuse to sign this authorization, your health care and relationship with your provider and with TC will not be affected; however, you will not be able to enter this research study.
Note: We will use this information for research purposes only. Any information we get from you or your health records will be identified by a number only, not by your name.

1. If you sign this form, you are agreeing that TC may use and disclose protected health information collected and created in this research study.
2. The specific health information and purpose of each use and disclosure are:

Health Information (Check as applicable)	**Purpose(s)** (Enter matching letter(s) from Purpose Categories)
√ Medical records	**____A, E, J**
√ X-ray/MRI/CT/Diagnostic Images	**____A, C, D, F, I, J**
√ Photographs, videotapes, or digital or other images	**____ A, C, D, F, I, J**
√ Questionnaires, interview results, focus group survey, psychology survey, behavioral performance tests (e.g., memory & attention)	**___ A, C, D, F, I, J**
__ Other:	

Purpose Categories

a. To learn more about the condition/disease being studied
b. To learn more about the costs of treating the condition/disease being studied
c. To improve health care for persons with the condition/disease being studied
d. To analyze research results
e. To facilitate treatment, payment, and operations related to the study
f. To complete research obligations in this study
g. To comply with federal or other governmental agency regulations
h. To monitor for adverse events/side effects
i. To determine the safety and effectiveness of the treatment(s)
j. To perform quality assessments related to research at TC
k. To teach TC students
l. To place in a repository or "bank" for future research purposes

3. If the information to be used or disclosed contains any of the types of records or information listed below, additional laws relating to use and disclosures of the information may apply. You understand and agree that this information will be used and disclosed only if you place your initials in the applicable space next to the type of information. *(Investigators please type N/A in irrelevant fields).*
   - _N/A AIDS or HIV infection information
   - _N/A Drug/alcohol diagnosis, treatment, or referral information
   - _N/A Mental or behavioral health or psychiatric care
   - _N/A Genetic testing information
4. The persons who are authorized to use and disclose this information are:
   - √ All the investigators listed on page one of the Research Consent Form
   - √ Others at TC who are participating in the conduct of this research protocol:
   - √ The TC Institutional Review Board
5. The persons who are authorized to receive this information are:
   - N/A The sponsor of this study:
   - N/A_ Federal or other governmental agencies responsible for research oversight:
   - N/A_ Others:
6. Protected health information that we collect from you in this study will be kept by us until:
   - √ The study is completed
   - ___ Indefinitely
   - ___ Other:
7. You have the right to revoke this authorization and can withdraw your permission for us to use your information for this research by sending a written request to the Principal Investigator listed on page one of the research consent form. If you do send a letter to the Principal Investigator, the use and disclosure of your protected health information will stop as of the date he/she receives your request. However, the Principal Investigator is allowed to use information collected before the date of the letter or collected in good faith before your letter arrives. Revoking this authorization will not affect your health care or your relationship with TC.
8. If we have disclosed your protected health information outside of TC, to persons or agencies identified in item #5 above, it is possible that this information could be released again without your permission. TC tries to protect against this by being very careful in releasing your information. The ways in which we will limit the further release of your protected health information are:
   - __ Contractual agreements with those who may not receive the information
   - √_ Not releasing your information in a way that could identify you
   - __ Other: We will use this information for research purposes only. Any information we get from you or your health records will be identified by a number only, not by your name.

You will receive a copy of this authorization form after you sign it.

_____

Printed name of research subject or subject's representative

_____ _____

Signature of subject or subject's representative Date

Description of Relationship to subject: _____

This HIPAA Research authorization form must be used exactly as it is presented here. Any alteration or editing of the form will render it unapproved for research use at TC. The use of an unapproved research consent /authorization form will require that any data collected from subjects who received such a form, must be excluded.