Dysphagia Assessment and Intervention for Individuals with Huntington's Disease

A Thesis Submitted in Partial Fulfilment of the Requirements for the

Degree of Doctor of Philosophy

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November 2020

Abstract

Huntington's Disease (HD) is a progressive neurodegenerative disease characterised by cognitive, motor and behavioural impairments. Corticobulbar symptoms have been reported in all stages of HD, and aspiration pneumonia associated with swallowing impairment (dysphagia) has been identified as the most common cause of death. Current literature examining interventions to treat or rehabilitate dysphagia in HD is limited; therefore, conventional treatment consists of compensatory techniques to maintain weight and minimise the risk of aspiration. There is emerging multidisciplinary research to suggest that intensive rehabilitation may improve or maintain function of corticospinal symptoms in HD. It has not yet been documented if these changes are evidenced in corticobulbar systems. This research addresses substantial gaps in the literature in respect to evaluation of dysphagia associated with HD, and furthermore evaluates an innovative skill-based dysphagia training protocol in individuals with HD.

The research programme is comprised of three elements. The first was a systematic review of the existing evidence relative to rehabilitation of corticobulbar symptoms associated with HD. Relevant electronic databases were systematically searched for literature related to corticobulbar rehabilitation in HD. The eight studies which met the inclusion criteria were evaluated using standardised critical appraisal tools. The best available evidence was limited by a high risk of bias and a lack of validated and objective outcome measures of corticobulbar symptoms. This systematic review documented a lack of evidence to support the use of rehabilitation to treat corticobulbar symptoms in HD. However, the suggestion of potential positive effects and no adverse effects reported in the limited literature provided justification for further research in this area. For continuity, this systematic review has been included as part of this thesis literature review. The published manuscript can be found in Appendix A.

Although instrumental assessments have been used in a limited number of studies to describe the manifestation of dysphagia in individuals with HD, no research exists regarding the reliability of these measures in this population. The second section of this research was a methodological study which evaluated the reliability and variability of existing measures to assess dysphagia in individuals with HD. Ten individuals diagnosed with symptomatic HD including dysphagia were recruited. Participants underwent instrumental and clinical assessments of swallowing function and biomechanics on three separate occasions over one week. Objective measures of functional swallowing included the Timed Water Swallow Test (TWST) and Test of Masticating and Swallowing Solids (TOMASS). Swallowing biomechanics were measured using manofluoroscopy and ultrasound assessments. Test-retest reliability was evaluated for each measure using Type 3 intraclass correlation coefficient (ICC (3,1)). Results indicated good to excellent reliability (> 0.75) in 5/7 parameters of the functional assessments (TWST/TOMASS) and moderate to excellent reliability (> 0.5) in 4/6 ultrasound measures. Manometric measures produced poor test-retest reliability (< 0.5). Videofluoroscopy measures ranged from poor to moderate reliability (< 0.5 to < 0.75). These data documented mixed reliability for measurement of swallowing in HD. The quantified reliability and variability in this data can be used in selecting and interpreting outcomes in subsequent intervention studies. This research addressed the ongoing need for critical evaluation of the reliability and anticipated variability of swallowing outcome measures in individuals with HD.

The final section of this research programme was an exploratory treatment study which investigated the feasibility and effectiveness of a skill-based swallowing rehabilitation paradigm for individuals with swallowing impairment secondary to HD. Twelve individuals diagnosed with symptomatic HD including dysphagia completed ten sessions of daily skill-

based dysphagia therapy in two weeks using Biofeedback in Strength and Skill Training (BiSSkiT) software and surface electromyography hardware. The software incorporated skill training approaches to improve participant's volitional control in manipulating the timing and amplitude of the submental muscles involved in swallowing. This intensive intervention, based on the principles of motor learning, aimed to maximise early neural re-organisation reported in HD and enhance cortical modulation to improve the safety and efficiency of swallowing. A within-subject A-B-A study design was utilised to include two-week blocks of no treatment pre-therapy as baseline and post-therapy for retention. Swallowing was evaluated using the TWST, TOMASS, manofluoroscopy, ultrasound and the Swallowing Quality of Life Questionnaire (SWAL-QoL). All participants completed the intervention protocol and improved in task performance over the two-weeks of training. A significant improvement in quality of life was reported post-therapy ($p < 0.05$) and maintained two-weeks post-treatment. There were significant treatment effects observed as liquid bolus transit times increased and upper oesophageal sphincter (UES) distension decreased post-therapy ($p < 0.05$). These changes were not maintained during the non-treatment post-therapy period. This study provided preliminary evidence that this intensive skill-based training is a feasible option with no adverse effects in individuals with HD. However, there were limited data to suggest this intervention protocol significantly altered swallowing biomechanics in this patient cohort. This is the first study to evaluate the effectiveness of dysphagia rehabilitation using instrumental swallowing outcomes in HD; therefore, further evidence is required to evaluate treatment protocols according to swallowing characteristics and disease stage.

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Please detail the nature and extent (%) of contribution by the candidate:

E Burnip was the primary author of this manuscript (90%); M-L Huckabee, K Gozdzikowska and E Wallace developed the concept of the manuscript and all contributed to manuscript editing (40%). E Burnip and E Wallace completed the systematic review and data extraction (70%), M-L Huckabee and K Gozdzikowska contributed to evaluation and data extraction (30%).

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Name: *Maggie-Lee Huckabee PhD* Signature: Maggie-Lee Huckabee Date: *13.11.20*

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Chapter 5.4: Dysphagia Rehabilitation (Skill-based dysphagia training)

Huckabee, M. L. & ***Burnip, E.*** *(2018). Still rethinking rehab: Motor learning treatment approaches for dysphagia. American Speech Language-Hearing Association SIG 13. 3, 146- 156.*

Please detail the nature and extent (%) of contribution by the candidate:

M-L Huckabee conceptualised the manuscript, E Burnip completed the literature review and critical appraisal (70%), M-L Huckabee compiled the manuscript. Both authors contributed to manuscript editing. E Burnip conceptualised the skill-training model included in the manuscript.

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Name: *Maggie-Lee Huckabee* Signature:  Date: *13.11.20*

Acknowledgements

I would firstly like to express huge gratitude for my supervisor Prof. Maggie-Lee Huckabee. Your incredible knowledge, experience and determination to 'fix' swallowing inspired me to complete my doctoral research at the Rose Centre. I have developed personally, professionally and learned so much under your supervision. I am very thankful for the many opportunities and experiences I have been fortunate to have over the last few years. I would like to extend my thanks to my second supervisor Dr Kristin Gozdzikowska. Thank you for sharing your brilliant knowledge, problem-solving and reassurance through this process. You have always been there for me as a tremendous support and mentor.

I would like to express huge thanks to all patients, families and members of the HD Associations for generously offering your time and effort to take part in these studies. It was an honour and a pleasure to meet every individual and get to know you over several visits. I would like to offer special thanks to Maggie Jury and Jo Dysart who are dedicated to supporting individuals and families affected by HD. I would like to acknowledge the financial support from the HD Associations, St George's Hospital and the University of Canterbury for enabling me to pursue this degree and the Neurological Foundation of New Zealand for their valuable financial contribution to allow us to undertake this research. I would also like to express my gratitude to Becca Hammond, the Speech Therapy Department and Radiology staff at North Shore Hospital. I wish to acknowledge Dr Richard Roxburgh and Dr Christina Buchanan at Auckland Enroll-HD study and Neurogenetic clinics for their interest and referrals.

I would like to express my sincere gratitude to Esther Guiu Hernandez, for your valuable contributions to this research. You have inspired me both personally and professionally with your kindness, patience and intelligence. I truly value your friendship, ongoing encouragement

and belief in my abilities. Further, to Dr Phoebe Macrae, I am constantly impressed by your knowledge, critical thinking and equally critical questions. I am grateful for your time, valuable advice and input into this programme. It has been an honour to be part of such an incredible team of people all united by Maggie-Lee's passion to do better for our patients and discover new things. A special thanks to my fellow doctoral students Paige Thomas, Emma Wallace, Katharina Winiker, Karen Ng, Seh Ling Kwong, Djiana Dragicevich, Keri Darrock, Eloise Smith and Marion Girod-Roux and all of the other students who have passed through the Rose Centre. Particularly to the world-class interns Anna Gillman, Lauren McIntosh and Gabby Chessells who were keen to learn and invaluable during data collection. I treasure all of the laughs, tears, nerves, hugs, terrible jokes, disappointments, celebrations and cups of tea shared together. To Eric, Lucy and Fiona, I'm very proud to have called you my colleagues. Thank you to the librarian Margaret Paterson for your friendly and helpful advice. A special thanks to Paige's parents for adopting me during data collection.

Whilst I never thought I would be finishing my PhD studies during a global pandemic, my family and friends at home have always offered support and belief in me throughout this process. I would like to offer special thanks to my amazing parents Colin and Del, and my Grandma Betty. You have provided unwavering support and have always encouraged me to follow my dreams, even if they take me far from home. Finally, thank you to my very understanding and supportive partner Charlie. I am very lucky to have you and our wonderful friends by my side.

Every step of this research was inspired by my Uncle Glenn. I hope in some small way I have made you proud.

Table of Contents

Preface

This PhD thesis conforms to the referencing style recommended by the American Psychological Association Publication Manual (7th ed.) and spelling recommended by the Oxford Dictionary (https://www.oxforddictionaries.com). The research for this thesis was carried out between February 2017 and November 2020, while the candidate was enrolled in the Department of Communication Disorders at the University of Canterbury. The research presented in this thesis was carried out at the University of Canterbury Rose Centre for Stroke Recovery and Research at St George's Medical Centre, Christchurch and North Shore Hospital, Auckland. The research was supervised by Prof Maggie-Lee Huckabee and Dr Kristin Gozdzikowska and supported by a supervisory committee Esther Guiu Hernandez and Dr Phoebe Macrae. This research was completed with support from the University of Canterbury Connect St George's Hospital Doctoral Scholarship, University of Canterbury Doctoral Scholarship and a Small Project Grant from the Neurological Foundation of New Zealand. This PhD also included collaborations and data collection for other PhD research projects.

Conference Presentations:

- Presentation at the 7th European Society for Swallowing Disorders (ESSD) and World Dysphagia Summit (Barcelona, Spain, September 2017) Awarded 'Poster of Merit'
- Workshop presentation at the international Stroke Rehab: From No-Tech to Go-Tech conference, (Christchurch, New Zealand, January 2018)
- Presentation at the international Stroke Rehab: From No-Tech to Go-Tech conference, (Christchurch, New Zealand, January 2018)
- Presentation at the European Huntington's Disease Network Plenary Meeting (Vienna, Austria, September 2018)

- Presentation at Biomouth Multi-disciplinary Conference (Christchurch, New Zealand, October 2018)
- Presentation at the Huntington's Disease Association (South Island, New Zealand) Annual General Meeting (Christchurch, New Zealand, June 2019)
- Platform presentation at the 9th European Society for Swallowing Disorders Congress (September 2019, Vienna, Austria)
- Platform presentation at the 10th European Society for Swallowing Disorders Congress (October 2020)

Publications generated as part of this PhD:

- Huckabee, M. L. & **Burnip, E.** (2018). Still rethinking rehab: Motor learning treatment approaches for dysphagia. American Speech Language-Hearing Association SIG 13. 3, 146-156.
- **Burnip, E**., Wallace, E., Gozdzikowska, K., & Huckabee, M. L. (2019). A systematic review of rehabilitation for corticobulbar symptoms in adults with Huntington's Disease. *Journal of Huntington's Disease, 9*, 1-12.
- Winiker, K., **Burnip, E**., Guiu-Hernandez, E., & Huckabee, M. L. (2019). Validity of a pocket-sized ultrasound device in assessment of dysphagia. Submitted, in press.

Additional manuscripts being prepared from this research programme:

- **Burnip, E.,** Thomas, P., Guiu-Hernandez, E., Gozdzikowska, K., & Huckabee, M.L. (in prep) Test-retest reliability of swallowing outcome measures in Huntington's disease.
- **Burnip, E**., Thomas, P., Winiker, K., Guiu-Hernandez, E., Gozdzikowska, K., & Huckabee, M. L. (in prep). Skill-based dysphagia training as an intervention for individuals with Huntington's Disease.

Other collaborative projects:

- Huckabee, M. L., **Burnip, E**., Macrae, P., Greig, L., Guiu-Hernandez, E., & Knapp, E. (2018). The PERC Programme: Brewing Rehab Innovations Together. Presentation at Biomouth Multi-disciplinary Conference, Christchurch, New Zealand (October 2018).

- Winiker, K., **Burnip, E.**, Guiu-Hernandez, E., & - Huckabee, M. L. (2018) Reliability of ultrasound measurement for swallowing assessment. Presentation at Biomouth Multidisciplinary Conference, Christchurch, New Zealand (October 2018).
- Thomas, P., **Burnip, E.**, Troche, M., & Huckabee, M. L. (2018) Prolonging Swallowing and Quality of Life in Motor Neurone Disease through Skill Training. Presentation at Biomouth Multi-disciplinary Conference, Christchurch, New Zealand (October 2018).
- Winiker, K., **Burnip, E.**, Guiu-Hernandez, E., & Huckabee, M. L. (2019). Validity and reliability of a pocket-sized ultrasound device in assessment of dysphagia. Presented at the 9th European Society for Swallowing Disorders Congress, (September 2019).
- Thomas, P., Mossop, P., **Burnip, E**., Huckabee, ML. Patterns of Swallowing Skill Learning in Patients with Dysphagia as a Result of Motor Neurone Disease (MND). Presented at the 9th European Society for Swallowing Disorders Congress, (September 2019).

List of Abbreviations

ADLs	Activities of daily living
ANOVA	Analysis of variance
BA	Brodmann's area
BiSSkiT	Biofeedback in Strength and Skill Training
BoT	Base of tongue
CAG	cytosine-adenine-guanine sequence
CI	Confidence interval
CN	Cranial nerve
CNS	Central nervous system
CPG	Central pattern generator
CSE	Clinical swallowing evaluation
DOSS	Dysphagia Outcome and Severity Scale
DSG	Dorsal swallowing group
DTI	Diffusion tensor imaging
EAT-10	Eating Assessment Tool 10 Item
EMST	Expiratory muscle strength training
FA	Fractional anisotropy
FEES	Fibreoptic endoscopic evaluation of swallowing
fMRI	Functional magnetic resonance imaging
fps	Frames per second
HD	Huntington's Disease
htt	Huntingtin protein
HRM	High-resolution manometry
ICC	Intraclass correlation coefficient
IDDSI	International Dysphagia Diet Standardisation Initiative
LES	Lower oesophageal sphincter
LVC	Laryngeal vestibule closure
LRM	Low-resolution manometry
MD	Mean diffusivity
MDT	Multi-disciplinary team
MND	Motor Neurone Disease
MBSImP	Modified Barium Swallow Impairment Profile

MDTP	The McNeil Dysphagia Therapy Program
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NA	Nucleus ambiguus
NTS	Nucleus tractus solitaries
OT	Occupational therapy
PAS	Penetration-Aspiration Scale
PD	Parkinson's Disease
PCR	Pharyngeal constriction ratio
PEG	Percutaneous endoscopic gastrostomy
PT	Physiotherapy
QoL	Quality of life
RCT	Randomised control trial
SD	Standard deviation
sEMG	Surface electromyography
SLN	Superior laryngeal nerve
SLT	Speech-language therapist
SWAL-QoL	Swallowing Quality of Life Questionnaire
TOMASS	Test of Masticating and Swallowing Solids
TWST	Timed water Swallowing Test
VFSS	Videofluoroscopic swallowing study
VSG	Ventral swallowing group
UES	Upper oesophageal sphincter[1]
UHDRS	Unified Huntington's Disease Rating Scale
US	Ultrasound

[1] This thesis was prepared using British spelling conventions. However, direct quotes may contain American Spelling. Additionally, the acronym 'UES' (upper esophageal sphincter) is strongly represented in the literature, therefore UES rather than UOS (upper oesophageal sphincter) was used.

INTRODUCTION AND LITERATURE REVIEW

Chapter 1. Introduction

Swallowing dysfunction (dysphagia) frequently occurs as a result of neurodegenerative disease (Clavé & Shaker, 2015; Daniels, 2006; Dziewas et al., 2017b; Sasegbon & Hamdy, 2017). This symptom has a significant impact on quality of life (QoL), caregiver burden (Ekberg et al., 2002), and is often associated with medical complications including aspiration pneumonia (Ortega et al., 2017; White et al., 2008). Historically, neurodegenerative conditions such as Parkinson's Disease, Motor Neurone Disease and Huntington's Disease (HD) have had limited evidence to support dysphagia rehabilitation (Plowman, 2015). Compensatory strategies have been the primary intervention, with a presumption that intensive rehabilitation may be detrimental in these patient populations (Clarke et al., 2018; Hamilton et al., 2012; Hunt & Walker, 1989; Keage et al., 2020; Zimmerman et al., 2020). However, emerging evidence suggests that early rehabilitative interventions may be beneficial in slowing deterioration or even improving functional outcomes in HD (Quinn et al., 2020). This is an important area of research in both corticospinal and corticobulbar literature. This research programme focused on dysphagia associated with HD. Dysphagia is widely accepted as a universal symptom of this disease (Kagel & Leopold, 1992; Schindler et al., 2020), and is associated with aspiration pneumonia, the leading cause of death (Heemskerk & Roos, 2012). This research programme was inspired by a lack of active treatment approaches available in clinical practice, and the need to investigate potential options for early intervention when symptoms are first identified.

The first part of this thesis includes a literature review, including a detailed description of normal swallowing from cortical to peripheral control. There is a particular emphasis in Chapter 3 on reviewing methods to measure swallowing biomechanics, and how reliable these measurement techniques are in a complex neurodegenerative population such as HD. The

following chapters then describe the neurophysiology of HD in more detail, and how these physiological changes impact on swallowing. This leads to the first part of this research programme: a systematic review of the literature to evaluate any existing evidence in rehabilitation of corticobulbar symptoms of HD (including dysphagia). For continuity, this systematic review has been discussed throughout Chapter 5 which presents research to support current treatment approaches in HD. As limited evidence exists evaluating rehabilitation of dysphagia in HD, the final part of Chapter 5 includes recent research which has described positive effects of swallowing rehabilitation in other aetiologies. Chapter 6 compiles this review into an outline of research questions and hypotheses for the subsequent two studies of this research programme.

As the literature review highlighted that current evidence evaluating swallowing in HD is limited by a lack of standardised outcome measures, the initial research question was raised: which are the most reliable measures in this patient population? The second part of this research consisted of a methodological test-retest study which evaluated the reliability and variability of swallowing measures in a cohort of individuals with HD. This study aimed to identify the typical fluctuations in swallowing as measured by a wide range of behavioural and instrumental assessments. By quantifying the reliability and estimated variability of swallowing in this population, clinicians and researchers can critically analyse results of subsequent intervention to evaluate treatment effects with confidence.

The methodology and results of both the test-retest study and the treatment studies are reported in Chapters 7 and 8. This final study brings together several elements of this research programme to provide preliminary evidence regarding assessment and intervention of dysphagia in individuals with HD. The intervention study is the first in the world to evaluate

swallowing outcomes using standardised behavioural and instrumental assessments following skill-based dysphagia therapy in individuals with HD. The assumptions that skill training can change swallowing biomechanics and cortical activation had not been investigated in HD. To evaluate treatment effects on cortical connectivity, the outcomes of a single case study are described which included magnetic resonance imaging (MRI) of the brain pre- and post-therapy. This intervention study matches the current momentum within fields of HD and dysphagia research to establish early rehabilitation approaches aimed to slow deterioration, improve symptoms and optimise QoL for our patients. The results and clinical implications of both of these patient studies are discussed in Chapter 9. This research programme addresses the substantial gaps in current literature and clinical practice to provide a foundation for future research in dysphagia treatment in HD.

Chapter 2. The Swallowing Mechanism

Swallowing is a highly complex sensorimotor mechanism which involves at least 25 paired muscles of the head and neck, innervated by their respective cranial nerves (CN) (Jean, 2001). This fundamental task is crucial for both ingestion as the primary source of nutrition and hydration, as well as protecting the upper respiratory tract through effective clearance of the pharynx to avoid aspiration of foreign particles (Jean, 2001). Successful swallowing is represented by safe and efficient coordination of oropharyngeal mechanisms lasting approximately 0.6 to 1.0 s to ensure the bolus is transported from the oral cavity, through the pharynx, oesophagus and into the stomach (Doty, 1968; Kahrilas et al., 1996; Logemann, 1998). There are several levels of central to peripheral control to complete this complex biomechanical process, as discussed below.

2.1 Biomechanics of Swallowing

Swallowing involves muscles of the oral cavity, pharynx, larynx and oesophagus. Eight of the 12 cranial nerves of the peripheral nervous system are involved in deglutition (Jean, 2001). Of these, the trigeminal (CN V), facial (CN VII), glossopharyngeal (CN IX), vagus (CN X), and hypoglossal (CN XII) cranial nerves are crucial to relay sensorimotor information between the brainstem swallowing centres and the peripheral structures during swallowing (Perlman & Christensen, 2003). This biomechanical process incorporates a range of voluntary and involuntary elements (Leopold & Kagel, 1997). The understanding of ‘normal swallowing’ is a constantly evolving concept within this field of research; studies investigating swallowing in healthy adults have demonstrated significant variance both within and across participants (Humbert et al., 2018; Steele et al., 2019). Swallowing is adaptive to various conditions dependent on bolus viscosity, volume and type of swallowing response, such as sequential

swallowing, or saliva swallows during sleep (Daniels & Foundas, 2001; Logemann, 1998; Steele et al., 2019). The swallowing mechanism is often conceptualised into three phases; however, to acknowledge the significant influence of input prior to the oral phase (Leopold & Kagel, 1997), the process of deglutition will be described using four theoretical stages below. The phases are complex overlapping sequences. The innervations and durations of each phase are highly dependent on interneuronal connections incorporating sensorimotor feedback for precise and timely responses (Jean, 2001; Martin-Harris et al., 2005b).

2.1.1 The Pre-oral Phase

Inclusion of the pre-oral phase of ingestive swallowing is important in recognition of the cognitive, motor and sensory stimuli before the bolus enters the oral cavity. These factors interact with external environmental aspects and heavily influence individual mealtime behaviours. Cognitive or physiological impairments can impact the level of attention, awareness of hunger, level of inhibition, speed of eating and the overall safety of deglutition (Leopold & Kagel, 1997).

External or environmental factors that influence somatosensory preparation can have a significant impact on efficiency of swallowing. Pre-oral visual, sensory and cognitive information impacts the resulting oropharyngeal motor response. Deglutition typically begins as the olfactory nerve (CN I) and optic nerve (CN II) are activated and provide crucial sensory information regarding the smell and sight of the food before the bolus enters the oral cavity (Steele & Miller, 2010). This sensory input travels to associated cortical areas for cognitive processing and can stimulate saliva production, oral intake and swallowing (Design Council, 2012; Ebihara et al., 2005). Several examples of altered motor responses to external stimuli have been demonstrated in healthy individuals. Some smells, such as citrus, can excite the

central nervous system (CNS) for up to 90 min (Wahab et al., 2010); other olfactory input can over-excite the CNS and inhibit swallowing (Steele & Miller, 2010). Leopold and Kagel (1997) considered this pre-oral phase particularly important to assess in individuals with neurogenic conditions as the changes within the CNS associated with these conditions can evoke cognitive, psychological and pre-oral sensorimotor impairments. Sensory events occurring before the bolus has entered the oral cavity can influence the subsequent mechanisms and exacerbate swallowing dysfunction.

2.1.2 The Oral Phase

The oral phase is predominantly under voluntary control and involves preparation and transport of the bolus within the oral cavity. Continuous sensory feedback is crucial throughout this phase; information regarding bolus type, volume, taste and temperature feeds into motor programme formulation. Afferent information including taste, touch and thermal sensation from the tongue, oropharynx, palatine tonsils and faucal pillars integrates via the sensory nuclei of CN V, VII and IX located at the nucleus tractus solitarius (NTS) within the central swallowing centre (Jean, 2001; Perlman & Christensen, 2003). This sensory information influences the frequency and pressure of mastication, bolus placement, formation and transport posteriorly when entering the oropharynx (Lowell et al., 2008). Elements such as mastication are centrally controlled and can be influenced by sensory feedback. This is demonstrated during mastication of an unanticipated texture as the rhythmic motion automatically ceases, and the motor programme is adapted (Humbert & Joel, 2012).

Acceptance of the bolus occurs through relaxation of orbicularis oris (CN VII) and jaw opening is facilitated by active contraction of the geniohyoid (ansa cervicalis), anterior belly of the digastric and mylohyoid muscles (CN V); this movement is combined with the antagonist

relaxation of the temporalis and masseter muscles (CN V) and stabilisation of the hyoid bone (Perlman & Christensen, 2003). The intrinsic lingual muscles (CN XII) change the shape of the tongue to accept the bolus into a cupped midline. The bolus is controlled anteriorly within the oral cavity; adequate labial seal through contraction of orbicularis oris (CN VII) is required to avoid oral spillage. Glossopalatal approximation, a protective mechanism to prevent pre-swallow pharyngeal pooling, is initiated through activation of the pharyngeal plexus (CN IX and CN X) which contracts the palatoglossus, styloglossus (CN XII), posterior belly of the digastric and stylohyoid muscles (CN VII). This is one of the initial involuntary protective mechanisms of the swallowing response to prevent airway compromise (Daniels et al., 2019). The larynx and pharynx are at rest during this phase, and nasal breathing occurs (Logemann, 1998).

The position of the bolus within the oral cavity varies across individuals. During mastication, contraction of styloglossus, intrinsic lingual muscles and extrinsic lingual muscles (CN XII) re-centre the bolus between dentition. Adequate lingual control and buccinator muscle contraction (CN VII), prevents lateral sulci residual and manipulates the bolus into a cohesive shape. Contraction of the external pterygoids (CN V) allows for lateral mandibular movement during rotary masticatory cycles. These rhythmic cycles are sequenced with lingual movement manipulating the bolus into position, mixing with saliva to be broken down by dentition. Taste via CN VII travels directly to the NTS and is perceived with cortical processing within the insula and primary sensory regions (Hamdy et al., 1999).

Lastly, the oral phase involves bolus transport and propulsion which greatly influences timely initiation of the pharyngeal phase (Jean, 2001). Once bolus preparation is sufficiently complete, lingual approximation pushes the bolus against the hard palate to generate intra-oral pressure

and propel the bolus into the oropharynx. Deep proprioceptive receptors of the base of tongue (BoT) and oropharynx relay this sensory pressure information to the brainstem to initiate the pharyngeal phase motor program (Jean, 2001). During bolus transport, thicker and harder foods typically require greater pressure and more swallows to clear compared to the same volume of a thinner texture (Steele et al., 2019). These systemic adaptations of intra-oral pressures and bolus propulsion are highly influential in the efficient activation of subsequent phases of deglutition. Impaired sensory feedback from the oral cavity to the NTS can alter intrabolus pressures, delay pharyngeal pressures and result in inadequate hyoid excursion impacting on relaxation of the upper oesophageal sphincter (UES) (Steele & Miller, 2010).

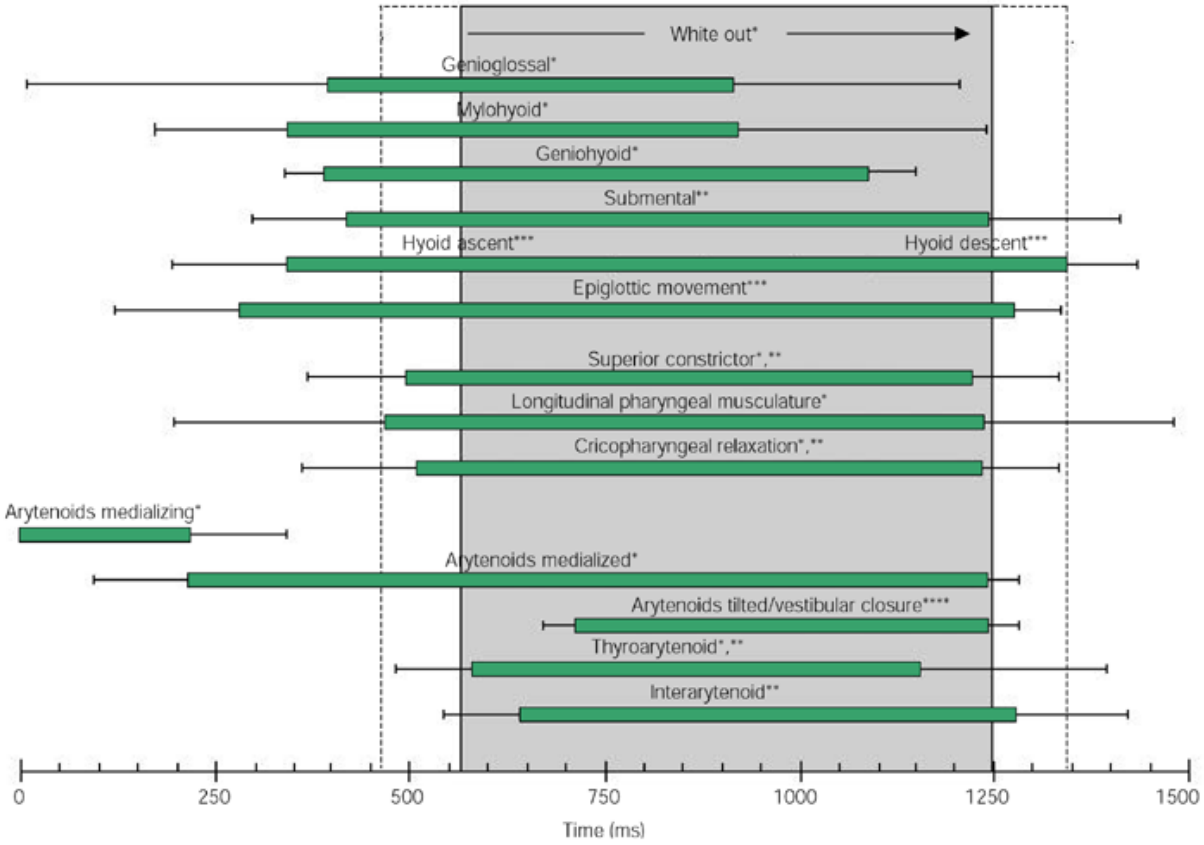
2.1.3 The Pharyngeal Phase

The sequenced activation of sensory receptors and muscle groups are crucial during the transition between oral and pharyngeal phases (Martin-Harris et al., 2008). Logemann (1998) described the onset of the pharyngeal stage as the moment the "leading edge of the bolus passes any point between the anterior faucial arches and the point where the tongue base crosses the lower rim of the mandible" (Logemann, 1998, p. 29). If the pharyngeal response was not initiated by this anatomical point, it was traditionally considered a delayed swallowing event. However, in healthy subjects, the anatomical level where the oral phase ends and the pharyngeal phase begins is highly variable both within and between individuals. Recent studies report that the bolus commonly accrues in the vallecula and may reach the level of the pyriform sinuses before the pharyngeal response is initiated in healthy individuals (Daniels & Foundas, 2001; Humbert et al., 2018; Steele et al., 2019). Once this initiation occurs at the end of the oral phase, the pharyngeal phase is typically considered reflexive due to the irreversible sequence of events that occur (Jean, 2001; Logemann, 1998); however, this 'all or nothing' response is modulated and adapts according to task and bolus type (Daniels & Foundas, 2001).

The leading biomechanical markers to indicate the onset of the pharyngeal phase are hyolaryngeal excursion (Nam et al., 2015) and arytenoid adduction (Langmore, 2006; Van Daele et al., 2005). This complex, yet rapid phase is characterised by both innervation and inhibition for groups of paired muscles. Figure 2.1 represents the temporal sequence of integral events during swallowing, including the sequence of muscle activation.

Figure 2.1

Representation of the Temporal Order of key Oropharyngeal Swallowing Events: Summarised from Studies Utilising Videofluoroscopy, Endoscopy, Needle Electromyography and Submental Electromyography



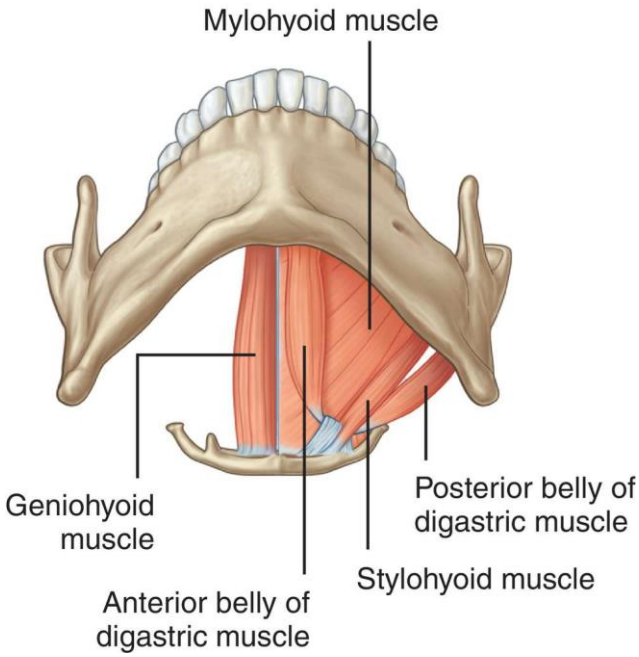
Note. Key: *McCulloch et al., unpublished data; **Perlman AL, Palmer PM, McCulloch TM, Van Daele DJ. Electromyographic activity from human laryngeal, pharyngeal and

submental muscles during swallowing. J Appl Physiol 1999;86(5):1663 - 1669. ***Perlman AL, Van Daele DJ. Simultaneous videoendoscopic and ultrasound measures of swallowing. J Med Speech Lang Pathol 1993;1(4):223–232. ****Shaker R, Dodds WJ, Dantas RO, Hogan WJ, Arndorfer RC. Coordination of deglutitive glottic closure with oropharyngeal swallowing. Gastroenterology 1990; 98:1478–1484. Note: Dashed and thin lines represent standard deviations. From: "Endoscopic evaluation of oral and pharyngeal phases of swallowing" by Langmore (2006). In R. Goyal & R. Shaker (Eds.), *GI Motility online* (para. 11). Nature. https://www.nature.com/gimo/contents/pt1/full/gimo28.html

As the bolus is propelled into the pharynx, activation of levator veli palatini (pharyngeal plexus) facilitates soft palate retraction to connect to the posterior pharyngeal wall and anterior bulging adenoid pad. This velopharyngeal closure seals off the nasopharynx, avoiding bolus redirection and contributes to the increased oropharyngeal pressure (Perlman & Christensen, 2003). During this period, hyolaryngeal excursion is completed. This movement is facilitated by contraction of the suprahyoid or submental muscles; specifically, the mylohyoid (CN V), anterior belly of the digastric (CN V) and geniohyoid muscles (ansa cervicalis) pull the hyoid anteriorly whilst the stylohyoid (CN VII) and posterior belly of the digastric (CN VII) pull the hyoid superiorly (Perlman & Christensen, 2003). The submental muscles integral for swallowing are depicted in Figure 2.2. Neural redundancy is observed as hyolaryngeal excursion is innervated by three cranial nerves (CN V, VII and XII) with three separate nuclei. Laryngeal elevation occurs through a combination of hyoid motion and contraction of the thyrohyoid muscles (ansa cervicalis). This superior movement of the thyroid cartilage during supraglottic shortening contributes to epiglottic inversion to complete aryepiglottic approximation (Logemann, 1998).

Figure 2.2

Anatomical representation of the suprahyoid or submental muscles in the inferior view



Note. Reprinted with permission from *Gray's Anatomy for Students: Third Edition*, (p. 1008) by Drake, R., Vogl, A. W., Mitchell, A. W. M., (2015), Churchill Livingstone Elsevier, Canada.

BoT retraction continues after the bolus has passed. Simultaneous contraction of the stylohyoid (CN VII), posterior belly of the digastric muscles (CN VII), hyoglossus (CN XII), genioglossus muscles (CN XII) and glossopharyngeus muscles (pharyngeal plexus) facilitates BoT contact with the posterior pharyngeal wall. This contact is important to ensure sufficient pressure is generated to drive the bolus through the pharynx. A combination of the BoT retraction and posterior bolus propulsion contributes to passive posterior horizontal inversion of the epiglottis. Pharyngeal shortening reduces the distance the bolus has to travel whilst reducing intraluminal area. Afferent fibres of CN IX are closely connected to the pharyngeal branch of CN X to form the pharyngeal plexus. Motor efferents of the pharyngeal plexus initiate symmetrical pharyngeal narrowing and shortening through innervation of the palatoglossus,

palatopharyngeus, salpingopharyngeus, levator veli palatini and uvular muscles. The superior and middle pharyngeal constrictors contract sequentially during pharyngeal shortening to clear the tail of bolus through the pharynx. The duration of the shortening increases with bolus volume and the greatest average displacement of 22 mm occurs at the pharyngeal area between the vallecula and superior margin of the arytenoids (Kahrilas et al., 1992).

There are several levels of airway protection, which again represent redundancies in the system to compensate for failures in the mechanism. The larynx is closed at four levels, typically described as an inferior reaction (bottom up response) within the supraglottic space (Vose & Humbert, 2018). These include true vocal fold adduction, approximation of false vocal folds, epiglottic deflection and anterior movement of the arytenoids to approximate with the base of the inverted epiglottis (Vose & Humbert, 2018). The onset of laryngeal closure through arytenoid medialisation is one of the first events of swallowing (Van Daele et al., 2005), however full adduction is not complete until after hyolaryngeal elevation. Two branches of CN X, namely the superior laryngeal nerve (SLN) and recurrent laryngeal nerve are critical to facilitate efficient LVC. The SLN conveys sensory afferents from the laryngopharynx, epiglottis, supraglottic laryngeal mucosa and aryepiglottic folds and the recurrent laryngeal nerve conveys subglottic sensation (Jean, 2001). LVC is considered complete at the moment of no visible airspace on VFSS, which represents contact between the arytenoids and the base of epiglottis with complete epiglottic deflection (Vose & Humbert, 2018). The upward response of true and false vocal fold adduction contributes to the expulsion of any materials in the laryngeal vestibule as an additional line of defence. Anterior tilting of the arytenoid cartilages by the aryepiglottic and lateral cricoarytenoid muscles cover up to half of the LVC. The inward rocking movement of arytenoid cartilages, and anterior superior laryngeal movement closes the laryngeal vestibule by meeting the thickened base of the epiglottis. The

corniculate and cuneiform cartilages within the arytenoids form additional protection as the bolus is re-directed to the lateral channels into the UES. Epiglottic deflection facilitates compression of the quadrangular membrane over the anterior glottis to protect the airway which also re-directs the bolus laterally. Finally, pharyngeal constriction manoeuvres the tip of the epiglottis to obtain full contact with arytenoid base (Vose & Humbert, 2018). Expiration immediately post-swallowing can be viewed as an additional level of airway protection to eject any residual bolus and prevent aspiration.

The events of LVC onset and duration are highly associated with UES opening and duration (Steele et al., 2019). Hyolaryngeal excursion combined with pharyngeal shortening and the oropharyngeal pressures driving the bolus facilitates opening of the UES (Logemann, 1998). The UES consists of the cricopharyngeus muscle, the inferior pharyngeal constrictors and rostral oesophageal musculature (Williams et al., 2001). At rest, the UES is contracted through tonic activation of the cricopharyngeus muscle. During the pharyngeal motor response, the UES has the greatest tension immediately prior to relaxation through innervation of the SLN (CN X) (Perlman & Christensen, 2003). A combination of cricopharyngeus muscle relaxation and laryngeal excursion contributes to UES opening and results in a drop in pressure at the UES. UES opening occurs earlier and increases in response to larger bolus volumes (Cock et al., 2017). As the larynx returns to rest position and lowers, the UES contracts and closes (Logemann, 1998).

2.1.4 The Oesophageal Phase

Unlike the striated muscles involved in the oral and pharyngeal phases of swallowing, the oesophageal phase is comprised of both striated and smooth muscle fibres. Striated muscles of the superior oesophagus are controlled by cranial motor neurones; the lower thoracic

oesophagus smooth musculature is controlled by the autonomic nervous system (Jean, 2001). The UES forms the superior boundary of the oesophagus. After the bolus travels through the UES, it then returns to a contracted tonic state of closure signalling the onset of the oesophageal phase (Cock et al., 2017). The bolus travels distally through the oesophagus via sequential peristalsis to the lower oesophageal sphincter (LES) which delineates the border of the oesophagus leading into the stomach. The LES is a muscular sphincter which, like the UES, relaxes during opening, and tonically contracts at rest. Typical timing of this phase can vary from eight to 20 s dependent on the bolus and amplitude of response (Dodds et al., 1973).

2.2 Neural Control of Swallowing

Swallowing was once considered a purely reflexive motor task, namely brainstem driven via bulbar lower motor neurones. However, more recent research has suggested that swallowing relies on complex and widespread neural connections within the CNS including cortical modulation (de Lima et al., 2015; Flowers et al., 2017; Wilmskoetter et al., 2020). This input can be conceptualised as a reciprocal cycle of planning and modulation involving several cortical, subcortical and peripheral regions.

2.2.1 *Brainstem Control of Swallowing*

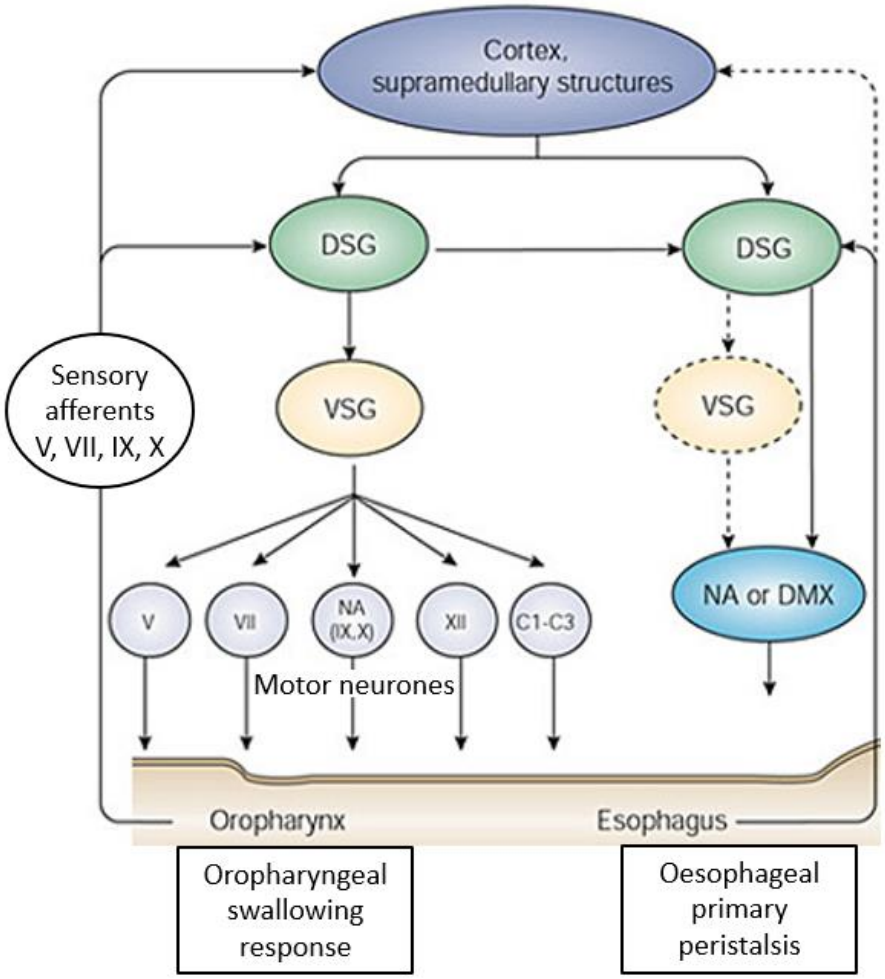
The brainstem is well-documented as key in the biomechanical response during voluntary and involuntary deglutition (Avivi-Arber et al., 2011; Doty, 1968; Flowers et al., 2011; Jean, 2001; Jean & Dallaporta, 2006). The construct of highly synchronised, bilateral central pattern generators (CPGs) have been proposed which consist of three sets of neurones: afferent neurones, efferent neurones and interneurons (Jean & Dallaporta, 2006; Miller, 2008). Afferent neurones transport bilateral sensory information from peripheral and subcortical input. The motor neurone efferents are activated in response to stimulation of the motor nerves.

Interneurons connect two groups of neurones within the medulla: the dorsal swallowing group (DSG) which includes the NTS and other neurones located in the dorsal medulla, and a ventral swallowing group (VSG), located in the ventrolateral medulla (Jean 2001). The DSG consists of bilaterally distributed generator neurones and adjacent reticular formation to initiate and shape the timing of sequential or rhythmic swallowing programs. The VSG contains switching neurons including the nucleus ambiguus (NA) which synapse on the bulbar motor nuclei to distribute and execute the swallowing motor program via motor neurones (Lang, 2009). These linear networks of neurones are organized based on the rostrocaudal anatomy of the swallowing tract to innervate sequential activation of NA to drive the bilateral muscles (Jean & Dallaporta, 2006). Evidence to support the presence of a swallowing specific CPG can be observed as a human foetus can produce a primitive swallowing reflex at 12-weeks gestation in the absence of developed cortical and subcortical regions (Hooker, 1954).

The swallowing CPG receives descending input from the cerebral cortex and subcortical areas as well as ascending peripheral input as summarised in Figure 2.3 (Lang, 2009). Sensory feedback from peripheral receptors of the pharynx, larynx, and oesophagus is essential for preparing the CPG and inducing the motor sequence (Lowell et al., 2008).

Figure 2.3

Summary of Swallowing Afferent and Efferent Cortical, Brainstem and Peripheral Circuits



Note. DSG: dorsal swallowing group within NTS; VSG: ventral swallowing group in the ventrolateral medulla. The simplicity of the oesophageal circuit is noted with a direct synapse between the DSG and to the motor nuclei. NA: Nucleus Ambiguus, DMX: dorsal motor nucleus of CN X. Adapted from "Electrophysiologic characterization of the swallowing pattern generator in the brainstem," by Jean, A., & Dallaporta, M., (2006). In R. Goyal, & R. Shaker (Eds.). *GI motility online* (para. 23). Nature. https://www.nature.com/gimo/contents/pt1/full/gimo9.html

The sensory nucleus of CN V spreads through the brainstem from midbrain to the medulla (Jean, 2001). The sensory nuclei of CN VII, IX and X are located at NTS. This integrated sensory feedback synapses at the sensory nucleus of the pons and the NTS within the medulla to adapt the pharyngeal response (Humbert et al., 2013). The motor nuclei of CN V and VII are located in the pons and the motor efferents of CN IX, X and XII originate from the motor nuclei located in NA (Perlman & Christensen, 2003). The geniohyoid is innervated by ansa cervicalis which consists of combined fibres of CN XII and anterior divisions of cervical spinal nerves 1 and 2. The extent of motor neurone participation and innervation of the peripheral musculature is dependent on afferent stimuli modulating the motor program generated by NTS. This motor program is transferred as part of the CPG circuits from the DSG to the VSG activating the key motor efferents of all motor nuclei involved in oropharyngeal swallowing (Jean & Dallaporta, 2006; Lang, 2009).

Primitive reflexive swallowing, such as swallows occurring during sleep, is an example of a centrally generated, predictable patterned response in the absence of external feedback. In contrast, ingestive swallowing utilises extensive sensory input for efficient and precise motor output. Sensory afferents from the oral cavity, pharyngeal and laryngeal anatomical regions transmit crucial information to their respective primary sensory nuclei within NTS. Integration of tactile or chemical stimulation from peripheral afferents by NTS has demonstrated increased excitability of the swallowing motor cortex (Martin et al., 2001). Animal studies have demonstrated that the SLN (CN X) has direct innervation of NA to initiate a sequential pharyngeal motor response in the absence of cortical input (Lammers et al., 2020; Lang, 2009). Although the brainstem driven CPG response is crucial for deglutition, the role of cortical modulation has been demonstrated by the presence of dysphagic symptoms in the absence of brainstem or lower motor neurone damage (Travers, 2009; Wilmskoetter et al., 2020).

2.2.2 Cortical Regions Activated During Swallowing

Understanding swallowing neural control was made possible by functional imaging, as well as clinical and animal studies utilising several methods to investigate central activation during swallowing. Recent advances in functional brain-imaging studies with healthy participants have proven critical in the evolving understanding of cortical involvement during different voluntary or automatic swallowing tasks (Humbert & Robbins, 2007).

Ingestive swallowing requires input from several cortical and subcortical regions which begin during the oral-preparatory phase. Diffuse activation during deglutition makes it difficult to distinguish exact cortical regions responsible for initiation or modulation of specific feeding behaviours (Huckabee et al., 2003; Travers, 2009). Environmental cues, including visual and olfactory input, are integrated with cortically driven behavioural factors such as attention (frontal lobes), emotion (limbic system) and memory (temporal lobes). This input into the association cortices is processed across several cortical regions and travels within bilateral ascending and descending sensory, motor and interneuronal pathways to the CPG for programming and regulation of the swallowing response (Ebihara et al., 2014; Jean, 2001; Leopold & Kagel, 1997; Martin et al., 2001; Michou & Hamdy, 2009; Wilmskoetter et al., 2020).

Research utilising fMRI techniques in humans has reported activation of the primary motor cortex in up to 80% of participants during natural, subconscious saliva swallowing (Martin et al., 2001). A systematic review by Humbert and Robbins (2007) reflected these results and reported bilateral activation of both primary and sensory motor regions during automatic swallowing. Specifically, activation of the precentral gyrus (primary motor and premotor

cortices), insula and post central gyrus (primary somatosensory cortex) were most prevalent across the literature (Humbert & Robbins, 2007; Wilmskoetter et al., 2020). The premotor cortex, which medially houses the supplementary motor area, has widespread connections to the basal ganglia; these neural pathways are integral for development and refinement of voluntary motor programs (Martin et al., 2001). The insula contains the gustatory and olfactory cortices and has connections to the precentral gyrus to modulate motor functions (Tian & Zalesky, 2018). The insula also receives widespread cortical input from the frontal, parietal and temporal cortical regions associated with the primary motor and sensory cortices to mediate several sensory and motor aspects of the aerodigestive tract including swallowing and motor speech (Martin et al., 2001). Unlike the insula, which is reported to be active during both voluntary and involuntary swallowing, bilateral activation of the caudal anterior cingulate gyrus is more associated with voluntary saliva and bolus swallowing. This activation facilitates the completion of the targeted motor task through processing the sensory stimuli and generating the response (Martin et al., 2001).

It is suggested that each progressive phase of swallowing is less dependent on cortical or basal ganglia modulation and becomes an increasingly brainstem-driven response (Jean, 2001; Leopold & Kagel, 1997). In both healthy and patient studies, bilateral cortical activation during swallowing has been reported (Humbert & Robbins, 2007; Martin et al., 2001); however, some evidence suggests the probability that one hemisphere is more dominant (Hamdy et al., 1999). This hemisphere dominance could present the potential for neural reorganisation of cortical control of swallowing in the event of cortical damage (Humbert & German, 2013; Wilmskoetter et al., 2020). This plasticity could be harnessed with targeted rehabilitation to promote more diffuse representation of swallowing across cortical regions to compensate and maintain function (Daniels et al., 2019; Humbert & German, 2013).

Subcortical structures are likely involved in initiation, monitoring and refinement of both voluntary and reflexive motor responses through processing of somatosensory feedback (Lowell et al., 2008). The basal ganglia has widespread cortical connections and processes somatosensory afferent information to influence the motor programs (Suntrup et al., 2012). Lesions involving the basal ganglia and internal capsule regions have a high incidence of dysphagia (> 75%) characterised by reduced efficiency of the motor response (Suntrup et al., 2012; Wilmskoetter et al., 2020). In neurodegenerative diseases caused by dysfunction within these basal ganglia pathways, both voluntary and involuntary swallowing can be affected. More research is required to fully understand the role of structures such as the internal capsule, subthalamus, amygdala, hypothalamus, substantia nigra, putamen, globus pallidus and cerebellum during swallowing (Flowers et al., 2011; Humbert & Robbins, 2007; Leopold & Kagel, 1997). However, evidence has shown the interaction between cortical and subcortical regions is crucial for precise and efficient swallowing (Flowers et al., 2017; Leopold & Kagel, 1997; Wilmskoetter et al., 2020).

Chapter 3. Assessment of Swallowing

The complexity of the swallowing mechanism in healthy individuals has been described in Chapter 2. It is well reported that factors such as age, gender and swallowing condition produce different responses in amplitude and timing (Hiss et al., 2004; Logemann et al., 2000; Steele et al., 2019); therefore clear parameters of normal and disordered swallowing are inherently challenging to determine based on varied assessment techniques and methods of measurement. Accurate assessment and understanding of swallowing biomechanics is vital for differential diagnosis and targeted management of dysphagia. The accuracy of assessment is dependent on instrumentation and available tools to measure swallowing. Swallowing assessments are often limited by utilisation of unreliable measures, subjective variation and inconsistency of methods. Thus, misunderstanding of impairment can lead to misdiagnosis, inaccurate reporting and poorly targeted intervention. It is crucial for clinicians to consider the validity, reliability and feasibility of assessment methods for each patient.

Validity is the extent to which an assessment accurately measures what it is intended to, whether as a diagnostic or screening tool. Swallowing assessment tools are considered to have higher validity if they have high sensitivity and specificity to correctly identify individuals who have dysphagia or are at risk of aspiration (Akobeng, 2007; Streiner, 2003). Sensitivity represents the proportion of people with the condition who receive a positive result. Specificity represents the proportion of people without the condition who receive a negative result. In swallowing screening and assessment, true validity is difficult to ascertain as the presence and parameters of impairment relies on comparison to imperfect and variable instrumental measurements (Giraldo-Cadavid et al., 2017).

Reliability of swallowing assessments can include several parameters, but overall high reliability refers to consistent, stable and replicable results when measuring the same parameters under the same conditions. Test-retest reliability, intra-rater reliability and inter-rater reliability are often reported in clinical research. Reliability is commonly quantified using the intraclass correlation coefficient (ICC). This method uses analysis of variance (ANOVA) and accommodates multiple raters and levels within the model to provide an estimate of variance (Downing, 2004; Weir, 2005). The ICC measures reliability as a ratio of variance between 0 and 1.0, values closer to 1.0 represent higher reliability (Weir, 2005). Generally, values > 0.8 are considered high, but this interpretation is dependent of the purpose of the assessment and consequences of the result (Downing, 2004). Reliability is affected by measurement acquisition referring to how the assessment has been administered, interpreted and extracted by the rater (Cook & Beckman, 2006). Test-retest reliability studies for measures of swallowing rarely separate these factors which could influence generalisability and clinical application. Inter-rater and intra-rater reliability should be clearly defined and reported (Downing, 2004).

Feasibility of an assessment or screening method is important as it can be a significant barrier to implementation of a valid and reliable evidence-based swallowing evaluation (Daniels et al., 2019). Feasibility regarding the cost, time taken, availability, discomfort, associated risks and general acceptability of that procedure for specific individuals is often influenced by clinician beliefs and service provision (Allen, 2019). The criteria and selection of the most appropriate assessment method depends on the clinician's goal of intervention, this may be for screening, diagnostic, reviewing or monitoring purposes. The availability of expertise, technology and measurements reported also varies depending on the setting, for instance in research

laboratories compared to routine clinical practice in public healthcare settings (Martin-Harris et al., 2017).

3.1 Observational and Behavioural Measures of Swallowing

3.1.1 Clinical Evaluation of Swallowing

There is widespread consensus that a detailed clinical bedside evaluation provides valuable information to identify individuals with dysphagia who may be at risk of aspiration (American Speech Language Hearing Association; Logemann, 1998). The clinical swallowing evaluation (CSE) typically includes non-instrumental, subjective measures of swallowing. This may include a detailed medical history, a comprehensive cranial nerve examination and oral trials (Logemann, 1998; McCullough & Martino, 2013). A thorough cranial nerve examination as part of the CSE provides valuable information regarding the function of cranial nerves integral for swallowing. Koch et al. (2017) validated their comprehensive cranial nerve examination and reported high sensitivity (0.89) and specificity (0.93) to identify swallowing impairment compared to instrumental assessment. However, standardised tools for completion of the CSE are limited in availability and infrequently utilised in clinical practice (McCullough et al., 2000). McCullough and colleagues (2000) reported that methods and measures employed during the CSE vary widely across clinicians and have insufficient intra-rater and inter-rater reliability across many parameters which is independent of clinician experience. In patients with neurogenic dysphagia, CSE has highly variable sensitivity (27% to 85%) and specificity (63% to 88%) to identify dysphagia compared to instrumental imaging methods (Bours et al., 2009). Further, CSE is problematic in terms of the inability to diagnose pharyngeal phase dysphagia or evaluate swallowing efficiency. In addition, it has consistently low sensitivity for identifying those at risk of aspiration across all patient populations (Coyle, 2015; McCullough & Martino, 2013; O'Horo et al., 2015). As the bolus cannot be directly visualised, an absent

cough response is not sufficient to rule out silent aspiration (Coyle, 2015). Clinical adjuncts to the CSE such as cough reflex testing could provide a clear protocol to identify patients with reduced sensorimotor integrity and risk of silent aspiration (Miles et al., 2013). The CSE provides valuable information to help the clinician hypothesise about possible impairments and guide the most appropriate instrumental assessment procedures (Coyle, 2015). Where possible, each aspect of the CSE should be integrated with instrumental assessment results to refine and formulate hypotheses regarding the pathophysiology of that patient and guide effective management (Daniels et al., 2019).

3.1.2 Timed Water Swallowing Test

To improve the replicability of subjective CSE, validated behavioural assessments of ingestion could be included to provide quantifiable assessment and monitoring of swallowing efficiency. Assessment of water swallowing is widely referenced in the literature as both a screening assessment and objective behavioural assessment of ingestion. In screening, qualitative judgements of the presence of overt signs of aspiration (including coughing or change in voice quality) are recorded. DePippo et al. (1992) evaluated the 3 oz water swallowing test as a screening tool in acute stroke patients; they reported high sensitivity of 94% and lower specificity of 26% in the detection of severe aspiration.

In contrast to swallowing screening, the additional quantification of time to complete the task allows for several parameters of swallowing efficiency to be calculated. The Timed Water Swallowing test (TWST) is a quick, easy and inexpensive assessment requiring readily available material. The patient is instructed to drink a measured cup of water (typically 100 ml or 150 ml) “as quickly as is comfortably possible” (Hughes & Wiles, 1996, p. 110). The time taken and the number of swallows (observed movement of the thyroid cartilage) are

documented and three quantified swallowing parameters are subsequently calculated: average volume per swallow, swallowing capacity and average time per swallow (Hughes & Wiles, 1996). The TWST has been reported as a valid and reliable measure of swallowing efficiency with established normative data for identification of patients with mild swallowing impairment (Hughes & Wiles, 1996; Nathadwarawala et al., 1992). Test-retest, intra-rater and inter-rater reliability were evaluated by six raters reviewing video recordings of neurological inpatients (n = 81) and healthy participants (n = 101) completing the TWST. A sensitivity of 96% and specificity of 69% were reported for the speed of swallowing measure (Nathadwarawala et al., 1992). Although the bolus or swallowing biomechanics cannot be directly visualised during the assessment, the TWST has been validated with VFSS in dysphagic patients with a reported sensitivity of 85% and specificity of 50% (Wu et al., 2004). Hughes and Wiles (1996) also demonstrated that the TWST is effective in identifying dysphagia in motor neurone disease (MND) as the specified parameters significantly differed compared to healthy participants. This assessment cannot inform differential dysphagia diagnosis, but sufficient evidence suggests it is a sensitive screening and assessment tool to inform clinicians of patient performance during ingestion of fluids (Ismail et al., 2019; Lin et al., 2002; Wu et al., 2004). This is a valuable quantitative aspect of the clinical evaluation which can be repeated, compared to normative data, and used for monitoring function in neurodegenerative populations.

3.1.3 Test of Masticating and Swallowing Solids

The Test of Masticating and Swallowing Solids (TOMASS), much like the TWST, provides objective measurement of swallowing ingestion that can be used for identification of impairment. Evaluation of mastication has previously been based on subjective clinical observations of dentition, oral control and timing. Alternatively, mastication can be measured

using objective techniques such as bite force, electromyography and infra-red video recordings which require specialist equipment and expertise (Hennequin et al., 2005). Impaired mastication, reduced orolingual pressures and ability to swallow a solid bolus are common in aetiologies with lower motor neurone involvement; moreover, oral phase dysfunction impacting on the pharyngeal phase has been identified in individuals with dysphagia and reduced cognition, such as dementia (Goodrich & Walker, 2019; Leopold & Kagel, 1997).

The TOMASS involves ingestion of a specified commercially available cracker. Patients are instructed to eat the portion of cracker "as quickly as is comfortably possible and when you have finished, say your name out loud" (Huckabee et al., 2017, p. 4). The time taken to finish the entire cracker, identified by the participant saying their name, is recorded. In addition, the number of discrete bites, masticatory cycles and observed swallows are collected. Extensive normative data are available from a series of studies accumulated by Huckabee and colleagues (2017). The authors reported high test-retest (ICC = 0.83 - 0.98) and inter-rater reliability (ICC > 0.98) with healthy participants and had high reliability when validated against instrumental measures of mastication (ICC = 0.99), respiration and thyrohyoid movement (ICC = 0.83). This is consistent with other literature validating objective measures of masticatory time and cycles against instrumental measures in healthy volunteers (Hennequin et al., 2005). Preliminary validation using surface electromyography (sEMG) measures of the masseter muscles also reported high correlation with masticatory cycles in patients with Parkinson's disease (PD) (Athukorala et al., 2014). Further validation of this measure in other aetiologies would be beneficial. The TOMASS provides a standardised method to evaluate the efficiency of solid bolus ingestion compared to international normative data.

3.1.4 Patient Reported Outcome Measures

Self-reported questionnaires can be valuable for the purpose of dysphagia screening and as adjuncts to clinical assessment. Several standardised patient reported measures are available for dysphagia screening, including the Eating Assessment Tool (EAT-10) and Sydney Swallow Questionnaire (McCullough & Martino, 2013). The EAT-10 is easily administered with ten items focused on the patient's perspective of the presence and burden of dysphagia symptoms (Belafsky et al., 2008). A cut off score of three or more indicates the risk of dysphagia requiring further assessment. Although the EAT-10 was not developed as a stand-alone screening tool, it has been validated for detection of dysphagia across various aetiologies (Belafsky et al., 2008; McCullough & Martino, 2013). Rofes et al. (2014a) validated the EAT-10 against VFSS instrumental assessment in patients referred with suspected dysphagia (n = 120), the authors reported 86% sensitivity and 68% specificity in detecting dysphagia compared to healthy controls (n = 14). The EAT-10 has now been validated in over 15 languages and multiple patient populations (Lechien et al., 2019). However, a recent evaluation of the psychometric properties of the EAT-10 identified weaknesses in the internal consistency and structural validity of the measure (Cordier et al., 2017). Therefore, this commonly utilised tool may not be sufficient as a stand-alone screening tool or outcome measure and should be interpreted in conjunction with other assessment methods.

Quality of life (QoL) assessment is an important aspect of swallowing evaluation as the psychosocial impact of dysphagia is associated with reduced QoL, self-esteem and increased burden (Ekberg et al., 2002). Self-reported QoL questionnaires are valuable tools to quantify the impact of dysphagia. There are several standardised patient-reported QoL measures specific to swallowing, such as the MD Anderson Dysphagia Inventory, Swallowing Quality of Life Questionnaire (SWAL-QoL) and the Swallowing Disturbance Questionnaire (Keage et al.,

2015). Many disease specific QoL questionnaires have also been developed for neurodegenerative diseases including PD, Multiple sclerosis, HD and MND. The SWAL-QoL consists of 44 questions divided into 10 domains (burden, eating duration, eating desire, food selection, communication, fear, mental health, social, sleep, and fatigue). Each question is scored on a five-point Likert scale and total scaled scores are calculated out of 100 (McHorney et al., 2002). The number of items which are used to represent each domain varies from two to five, therefore, domains such as social functioning are more weighted than food selection. Higher scores indicate better perceived QoL. The SWAL-QoL has been validated in several languages and can be self-administered or completed with a clinician. Clinical validity of the SWAL-QoL has been reported with significant correlations with VFSS oral transit time, total swallow duration and PAS in patients (n = 386) with dysphagia (McHorney et al., 2006). Evaluation of the SWAL-QoL test-retest, inter-rater and intra-rater reliability reported excellent internal consistency, reliability and stability (McHorney et al., 2002). It was also validated in patients with PD, those with identified dysphagia scored significantly lower compared to the non-dysphagic group (p = 0.02) (Plowman-Prine et al., 2009). Compared to other self-reported swallowing questionnaires, the SWAL-QoL takes longer to complete (approximately 15 minutes) which requires the patient to have sustained attention, a good level of literacy and adequate self-awareness. The increased clinical burden to complete the SWAL-QoL may limit the application of this tool into routine clinical practice (Keage et al., 2015). However, for research purposes, the SWAL-QoL has shown sufficient acceptability in terms of administration and sensitivity to detect change in neurodegenerative conditions and is frequently reported as a swallowing outcome measure (Athukorala et al., 2014; Ayres et al., 2016; Leow et al., 2010).

3.2 Imaging of Swallowing Biomechanics

Imaging techniques are essential for evaluation of swallowing, dysphagia diagnosis and treatment planning (Daniels et al., 2019; Inamoto & Saitoh, 2018). Clinicians and researchers rely on instrumental assessments to observe aspiration events, evaluate risk and understand the cause and effect of pathophysiology characterising the individual's swallowing performance (Inamoto & Saitoh, 2018). Recent technical advances have aided the development of several imaging methods of swallowing anatomy at rest and during swallowing (Allen, 2019). Methods include videofluoroscopy, computed tomography (CT), magnetic resonance imaging (MRI), endoscopy, ultrasound (US) and manometry. The most common swallowing assessments are videofluoroscopic swallowing study (VFSS) and fibreoptic endoscopic evaluation of swallowing (FEES) techniques (Inamoto & Saitoh, 2018).

3.2.1 Videofluoroscopy

Videofluoroscopic swallowing study (VFSS) is the most common instrumental assessment of swallowing biomechanics (Frowen et al., 2008). VFSS involves radiographic evaluation of the oral, pharyngeal and oesophageal phases of swallowing. Images can be collected in the lateral and anterior-posterior view. A bolus is combined with barium sulfate contrast agent (20% to 40% weight to volume ratio) to allow for visualisation through the aerodigestive tract (Martin-Harris et al., 2017; Steele et al., 2019; Stokely et al., 2015). Patients with suspected dysphagia undergo VFSS for evaluation of swallowing safety and efficiency, particularly individuals with neurological conditions or sensory impairments (Allen, 2019). VFSS provides visualisation of key events across the phases of swallowing, these include the extent and timing of hyolaryngeal excursion, epiglottic deflection, residual in the vallecula, pyriform sinus or pharynx (Allen, 2019; Martin-Harris et al., 2008). In addition to visualisation of swallowing biomechanics, the presence, timing and extent of ingested material entering the laryngeal vestibule (penetration)

or continuing below the level of the vocal folds into the trachea (aspiration) is evaluated during VFSS. The effectiveness of compensatory approaches such as diet modification or postural changes could also be evaluated during VFSS (Logemann, 1998).

The clinical environment and artificial structure of VFSS provides only a snapshot of conscious or cued swallowing, which may not be representative of typical unrestricted feeding behaviours (Inamoto & Saitoh, 2018). Limitations of this technique include radiation exposure, poor temporal resolution of assessments, subsequent movement artefacts and expertise and equipment required (Allen, 2019; Leonard, 2019b). At present, instrumental assessment of swallowing often relies on subjective interpretation of non-standardised protocols (Benfield et al., 2020). To improve accuracy and reliability of interpretation, there is a need for consistent use and understanding of quantitative measures implemented in both clinical and research settings.

3.2.1.1 Videofluoroscopic Spatial Measurements

There are various protocols and software applications described in the literature to obtain spatial and temporal measures of swallowing using frame by frame analysis of the video clips (Baijens et al., 2013a; Kim & McCullough, 2008; Leonard & McKenzie, 2006; Logemann et al., 2000; Molfenter & Steele, 2014; Sia et al., 2012). Spatial measures such as hyoid excursion, UES distention and pharyngeal constriction are frequently measured in research due to their highly predictive properties for increased risk of aspiration and pharyngeal residual in dysphagic patients (Easterling & Shaker, 2013; Kendall & Leonard, 2001; Leonard et al., 2011; van der Kruis et al., 2011). There is, however, lack of consensus about consistent methods to quantify swallowing parameters during VFSS (Steele et al., 2020; van der Kruis et al., 2011). The reliability of swallowing measures varies dependent on the methods utilised. Poor inter-

rater agreement in obtaining these measures raises questions about the validity of objective VFSS outcomes (Steele et al., 2020). Studies utilising semi-automatic computational analysis to measure pharyngeal constriction have reported the highest inter-rater reliability of all VFSS outcome measures (ICC = 0.92 - 0.99) (Leonard, 2019a; Schwertner et al., 2016). However, the trajectories analysed by this software did not provide kinematic measures to compare across assessments (Schwertner et al., 2016). Further, the stipulated coordinates to obtain this measure were visually inspected and adjusted by the raters which could inflate the high inter-rater reliability reported. This heterogeneity of methods to obtain the same quantitative measurements prevents direct comparison of raw data between studies (Sia et al., 2012).

3.2.1.2 Videofluoroscopic Temporal Measurements

VFSS can be conducted in continuous or pulsed modes. Thirty pulses per second is the standard and often referred to as continuous. Less than 30 pulses per second reduces the amount of radiation exposure but lowers the temporal resolution of the images (Mulheren et al., 2019). Given the speed of which oropharyngeal swallowing occurs, it is crucial that the screening rate is high to accurately visualise bolus flow and anatomical movement. Images should be captured at 30 frames per second (fps) to optimally identify timing events and calculate the relationship between events; < 15 fps is not sufficient to capture all temporal and spatial aspects of swallowing (Levine & Rubesin, 2017; Martin-Harris & Jones, 2008; Vose & Humbert, 2018), but 15 fps is most commonly used in clinical practice (Benfield et al., 2020). Although the optimal frame rate is 30 fps, this may be restricted to 25fps in some countries such as New Zealand due to mechanical restrictions within the radiological equipment. The difference between 30 fps and 25 fps equates to a difference of 0.01 s for each image captured. To what extent the difference in 5 fps would influence VFSS outcome measurements has not been evaluated; however, Mulheren and colleagues (2019) reported significant differences in bolus

transit times when comparing the same swallows of patients with acute stroke (n = 20) at 15 fps and 30 fps. The authors noted a trend for longer bolus transit times for thin fluids and pudding boluses with 30 fps but no significant differences in PAS ratings or inter-rater reliability (ICC > 0.95) for both frame rates (Mulheren et al., 2019).

Like the spatial measures obtained from VFSS, several methods exist for measurement of the temporal events within the literature. These methods include utilisation of anatomical reference points and biomechanical relationships, (Kahrilas et al., 1997) or a combination of swallowing response times compared to biomechanical events in response to bolus transport (Leonard, 2019a). Clinical application of these frame by frame analyses of swallowing sequence timings are seldom used in clinical practice (Martin-Harris & Jones, 2008). The lowest inter-rater reliability in dysphagic patients (K = 0.22 and K = 0.30) was reported for visuoperceptual judgements such as 'delayed' pharyngeal reflex (Baijens et al., 2011). It is important to acknowledge these common inaccurate observations and subjective judgements such as 'delayed swallowing' could affect differential diagnosis and evidence-based management (Baijens et al., 2011; Stoeckli et al., 2003).

These methods of measuring timing and displacement aspects of swallowing often require specialist equipment, expertise and can be time consuming (Martin-Harris et al., 2017). The development and implementation of standardised reporting methods are required to quantify the level of impairment. One example of a descriptive tool to quantify dysfunction is the Modified Barium Swallow Impairment Profile (MBSImP™©) (Martin-Harris et al., 2008; Martin-Harris et al., 2017). This tool requires specific clinician training and competency standards to ensure validity and reliability as reported in the literature (Martin-Harris et al., 2017). As certified programmes may be limited by training accessibility, 'in house' analysis

protocols are most frequently implemented in clinical practice (Benfield et al., 2020). The simplification of highly complex sensorimotor events using semi-objective ratings, as is involved in application of the MBSImP™©, may not be sufficient in order to measure change and does not quantify timing of events. For instance, judging LVC as 'complete', 'incomplete' or 'none' does not provide sufficient detail as a swallowing outcome measure (Frowen et al., 2008). Further peer review would be beneficial to evaluate to what extent the MBSImP™© descriptions reflect functional outcomes. Despite these inevitable limitations, standardised tools provide a framework for shared terminology across settings to improve the quality of reporting outcomes and allow for more meaningful comparison between assessments (Martin-Harris & Jones, 2008).

3.2.1.3 The Penetration Aspiration Scale

The most widely reported quantified measure of swallowing safety is the Penetration Aspiration Scale (PAS) (Rosenbek et al., 1996a). This eight-point scale provides a framework to rate the extent of airway invasion and biomechanical response in terms of attempted clearance during bolus trials, but fails to identify the pathophysiological cause of the invasion. PAS score of 1 or 2 are considered normal for healthy individuals (Allen et al., 2010; Garand et al., 2019; Humbert et al., 2018; Steele et al., 2019). Steele and Grace-Martin (2017) raised concerns about inconsistencies in the statistical application of the PAS as a research outcome and questioned the validity and sensitivity of each level. The authors called for a revision of infrequent levels such as PAS score of 6, to accommodate for clinically significant, sensitive changes between levels. Inappropriate use of statistical analysis of PAS results are common due to a lack of consensus regarding the statistical properties of the scale (Borders & Brates, 2019). Although intra-rater and inter-rater reliability are infrequently reported (Borders & Brates, 2019), the PAS has good reliability compared to other VFSS measures and remains a

clinically familiar, valuable tool widely used in dysphagia research to quantify airway invasion on VFSS (Benfield et al., 2020; Garand et al., 2019; Stoeckli et al., 2003).

3.2.2 Fibreoptic Endoscopic Evaluation of Swallowing

FEES consists of a flexible laryngoscope inserted transnasally and positioned in the hypopharynx in order to visualise the pharynx and larynx at rest and during swallowing (Langmore, 2017). This portable procedure is ideal for bedside instrumental assessments and allows for visualisation of bolus spillage, LVC, airway protection and pharyngeal residual (Langmore & Murray, 2013). FEES does not include evaluation of the oral phase of swallowing and images are obstructed by pharyngeal closure and bolus transit during the height of the swallow (Langmore, 2006). Although no standardised protocol exists for presentation or types of bolus trials in clinical practice, Langmore (2001) has described comprehensive guidelines for FEES examination which have yet to be validated. Pharyngeal sensation, secretions and post-swallowing residual can be rated, and postural or dietary compensatory interventions may be trialled (Langmore & Murray, 2013). Additionally, visualisation of the larynx may be utilised for biofeedback during training of compensatory strategies to improve understanding and accurate performance of the exercise (Langmore, 2017). The patient is not exposed to radiation during FEES; thus, the examination can be extended for evaluation of fatigue during oral trials. Re-assessments and reviews at multiple time points are possible to evaluate any changes in bolus flow (Langmore & Murray, 2013). Standardised outcome measures such as the PAS (Colodny, 2002; Rosenbek et al., 1996b), the Yale Pharyngeal Residue Severity Scale (Neubauer et al., 2015) and the Dynamic Imaging Grade of Swallowing Toxicity (Hutcheson et al., 2017) have been validated for quantifiable evaluation of swallowing efficiency and safety during FEES. Measurements obtained via FEES are often based on subjective observations of bolus flow or binary ratings of inferred pharyngeal dysfunction; therefore, the application of

FEES to assess rehabilitative outcomes is limited as direct measurements of swallowing biomechanics such as hyolaryngeal excursion and UES opening cannot be obtained.

3.2.3 Combined Assessment Techniques

A combination of assessment techniques such as a nasal cannula to measure respiratory airflow during VFSS or FEES may be beneficial to measure several aspects of respiratory-swallowing biomechanics within one procedure allowing for accurate diagnosis and treatment planning (Daniels et al., 2019; Martin-Harris et al., 2005a). Another example of mixed procedures is VFSS combined with pharyngeal manometry. Compared to VFSS or manometry alone, this combined assessment procedure increases patient burden and requires specialist synchronised equipment and expertise. This dynamic assessment does, however, improve temporal resolution with manometry to provide the highest level of diagnostic accuracy through understanding of swallowing biomechanics (Nativ-Zeltzer et al., 2012; Pal et al., 2003).

3.2.4 Pharyngeal Manometry

Manometric measures of pharyngeal swallowing have been available for several decades; however, clinical application has been slow as some only consider this assessment appropriate for severely dysphagic patients (Allen, 2019; Jones et al., 2014). On the contrary, manometry can be a valuable tool for clarifying signs and symptoms of swallowing dysfunction observed on VFSS as part of differential diagnosis. In cases where VFSS may be limited by poor temporal resolution, manometry provides quantitative measurements of the pharyngeal phase of swallowing. Using manometry, objective assessment of amplitude and duration of pharyngeal pressures, UES resting pressure and relaxation during deglutition can be assessed. These measures represent the relative coordination and efficacy of pharyngeal phase of swallowing useful for differential diagnosis, monitoring or as an intervention outcome measure

(Massey, 2013). Despite the significant advantages of this assessment and potential to guide suitable rehabilitative intervention, the equipment is not commonly available for clinical use, leading to low referral or demand even for patients with suspected UES dysfunction (Jones et al., 2014).

Evaluation of pharyngeal pressures during swallowing is conducted using low-resolution manometry (LRM) or high-resolution manometry (HRM). Both techniques utilise solid-state manometric catheters. LRM provides three sensors for measurement of pressure in the proximal pharynx, distal pharynx and UES regions. LRM has been used as a quantitative adjunct to fluoroscopic or endoscopic assessment of dysphagia in neurogenic populations such as stroke, MND, PD as well as other aetiologies (Butler et al., 2009; Winiker et al., 2019). LRM typically consists of three unidirectional sensors housed within a 2.1 mm catheter (Salassa et al., 1998). Massey (2013) commented that LRM equipment is cheaper than HRM, robust and is not limited by a maximum number of uses stipulated by the manufacturer. However, LRM sensors have limitations in terms of measuring only unidirectionally within the pharyngeal and UES lumen, and at fixed distances despite intra-swallow movement and anatomical variations across individuals (Castell & Castell, 1993).

Even though the radial direction of the unidirectional sensors has little impact on registered pressures (Hernandez et al., 2018), the placement of the manometric catheter must be consistent for interpretation and comparison across sessions (Salassa, 1999). The catheter is inserted through the nares according to standardised methods described by Castell and Castell (1993) and catheter standards recommended by Salassa et al. (1998). The exact point of sensor placement within the aerodigestive tract will vary dependent on the individual anatomy (Salassa et al., 1998). The peak amplitude and durational measures are of interest for

interpretation of the biomechanical sequence of events. Patients with an impairment of pharyngeal sequencing can be identified by reduced peak-to-peak latency between Sensor 1 and Sensor 2 peak waveforms representative of simultaneous or abnormal pharyngeal contraction (Huckabee et al., 2014).

A primary limitation of LRM compared to HRM is the accurate placement of the three sensors particularly the lowermost sensor in the UES. HRM data has highlighted substantial UES intra-swallow movement of up to 2 cm spanning across sensors (Massey, 2013; Pal et al., 2003). In addition, even when proximally secured, the manometric catheter ascends on average 0.5 cm during swallowing as a result of velopharyngeal closure and pharyngeal contraction (Pal et al., 2003). Several studies have reported normative data citing catheter placement using the identification of an 'M' wave as described by Castell and colleagues (1993) (Butler et al., 2009; Gumbley et al., 2008; Lamvik et al., 2014). Although this 'M' wave has never been validated, the waveform configuration is thought to represent resting pressure in the proximal UES at baseline, hyolaryngeal excursion moves the UES onto the sensor increasing resting pressure immediately before relaxation of the cricopharyngeus. In individuals with significant hyolaryngeal displacement, the reporting of inferred sensor location without concurrent radiographic imaging may reduce validity of measures (Salassa et al., 1998). LRM demonstrates sensitive variation in healthy subjects according to bolus type and swallowing condition (Al-Toubi et al., 2015; Butler et al., 2009; Gumbley et al., 2008). The stability of LRM timing and amplitude measures has been evaluated; there are no significant effects of trial or session in healthy adults (Butler et al., 2009; Hernandez et al., 2018; Hiss & Huckabee, 2005; Macrae et al., 2011). This level of temporal and amplitude sensitivity with high reliability allows for identification and diagnosis of abnormal swallowing biomechanics which directs treatment planning.

Whilst LRM is limited by three sensors, there have been advances in HRM technology which now houses 36 sensors. Advantages of HRM include quantitative measurement of the length of the pharynx and upper oesophagus; additionally, with an array of sensors, the UES can be measured despite natural movement during swallowing (Massey, 2013). HRM software provides averaged pressures across the sensors represented on contour plots with colour warmth depicting the pressure magnitude. These plots are visually intuitive for patient feedback and training, but representation of exact swallowing performance, sensor specificity and reliability for accurate diagnosis is questionable when using the colour plots alone (Massey, 2013). HRM is increasing in prevalence as a valuable adjunct to evaluate swallowing biomechanics in healthy individuals (Lan et al., 2017; Takasaki et al., 2011) and patient populations. HRM has been used to evaluate swallowing in patients with neurogenic dysphagia secondary to stroke (Lan et al., 2015), PD (Suttrup & Warnecke, 2016), MND (Takasaki et al., 2010) and a single case study in HD (Lee et al., 2012). Despite this increasing popularity, data collected from HRM catheters of up to 4.2 mm in diameter demonstrated higher pressure amplitudes and increased variability in healthy participants (Takasaki et al., 2008) compared to LRM normative data. In addition, higher resting UES pressures in patients with dysphagia and healthy participants (Xiang et al., 2013) have been reported as measured by HRM compared to LRM data. A recent systematic review by Winiker et al. (2019) highlighted inconsistencies in methodological implementation of HRM across research settings using either system-based software or customised external software which is not available for clinical application. This lack of agreement regarding the optimal methods of HRM analysis could impact the reliability and validity of HRM measures for consistent replication across studies. Other limitations which may increase the risk of measurement error have been highlighted,

these include general fragility of circumferential sensors and the incidence of baseline pressure drifts which can be affected by temperature (Lamvik et al., 2016; Massey, 2013).

3.2.5 Ultrasound of Swallowing

Ultrasound (US) evaluation of swallowing has been used in research for many decades to provide two-dimensional dynamic imaging of swallowing anatomy. US is a non-invasive method which can be applied to evaluate muscle morphology and swallowing biomechanics (Huckabee et al., 2015). US transducers emit high frequency sound waves ranging from 2.5 to 10 MHz which enter the organic tissue and are reflected back and converted to electrical signals to represent relative distances of tissue boundaries to the transducer (Aldrich, 2007). As the sound waves cannot travel through bony structures such as the mandible and hyoid, a visible acoustic shadow is cast allowing for identification of anatomical markers (Chi-Fishman, 2005).

Research has utilised US to investigate the structure, displacement and timing of the tongue, submental muscles, larynx, pharynx, hyoid and UES (Chi-Fishman, 2005). US imaging of the approximation of hyoid bone to mandible acoustic shadows has been used as a reliable and sensitive measure of hyolaryngeal excursion to identify significant differences between individuals with dysphagia and healthy controls (Hsiao et al., 2012; Huckabee et al., 2015; Macrae et al., 2012; Perry et al., 2016). Hsiao et al. (2012) and Chen et al. (2017) reported high reliability (ICC > 0.801 and ICC > 0.892 respectively) and strong correlations (r > 0.80) between US and VFSS measurement of hyolaryngeal excursion in dysphagic patients. Hammond (2019) has also reported significant correlations (p < 0.05) between US and VFSS measurements of hyoid excursion. These studies show valuable potential for the use of US but were limited by inadequate description of methods, for example, measurements were based on analysis of the ‘best’ images from three swallows; however, the final number of images

selected and how these were judged was not detailed (Chen et al., 2017). Hsiao and colleagues (2012) did not specify the criteria to select the frame of maximum hyoid excursion, and evaluation of inter-rater reliability was conducted on data from healthy participants which may not represent reliability of all measurements as part of the patient study (Hsiao et al., 2012; Huang et al., 2009). Further, the description of statistical analyses often failed not provide sufficient information to allow for replication or direct comparison across studies. Despite these methodological shortfalls, the sensitivity and specificity of US measurement of hyoid excursion as a predictor for patients who are at risk of aspiration has been reported as 84% and 81% respectively (Lee et al., 2016). In addition, hyoid excursion of < 1.5 cm was proposed as an indicator of patients who may require non-oral feeding with reported specificity of 73% and sensitivity of 66% (Hsiao et al., 2012).

Swallowing rehabilitation which aims to strengthen musculature integral to deglutition may target the submental and lingual muscles. US measurement of the cross-sectional area of the submental muscles in the coronal plane has been validated against MRI in healthy people (Macrae et al., 2013). Specifically, measures of the area of the left and right anterior belly of the digastric muscles were significantly correlated ($p < 0.01$) between US and MRI. Reliability of these rest measures of the submental muscles is better than the dynamic measures of hyoid excursion (Hammond, 2019; Macrae et al., 2012 ; Winiker, 2019). US measurement of these muscle groups can therefore be used to evaluate any hypertrophic changes as a result of therapy targeting isolated muscle strength (Huckabee et al., 2015); whether any changes in muscle mass results in changes to swallowing efficiency remains unclear.

US measures of swallowing have been reported in healthy people as well as patients with neurogenic dysphagia including stroke, PD and MND. Limitations of US include the within-

participant variability which is affected by the position of the transducer and participant posture (Chi-Fishman, 2005). Any changes in head or neck positioning can produce artefact and change US measures but use of a fixed transducer does not appear to improve measurement accuracy. Perry et al. (2016) reported less variability of measurement of the submental muscles using a hand-held transducer compared to a fixed transducer. Several methods of image acquisition and analysis have been reported leading to increased variability between raters (Winiker et al. 2020 in prep.). Further research is required for measurement refinement and development of normative data (Leonard, 2019a).

US has not translated to clinical practice as other imaging methods have, such as VFSS; however, with the recent advances in cheaper and smaller 'pocket-sized' devices, research focusing on clinical application is emerging. Two recent studies have evaluated the reliability and validity of the Clarius^{TM} 'pocket-sized' devices for measurement of several aspects of muscular morphology and anatomical displacement during swallowing (Hammond, 2019; Winiker, 2019; Winiker et al., 2020). In contrast to other literature, these studies reported poor to moderate (< 0.75) intra-rater and inter-rater reliability for measurements obtained online. Reliability improved when measurements were obtained offline. The authors hypothesise that these differences in acquisition and measurement may reflect environmental pressures, time constraints and technological difficulties impacting on the accuracy of image selection (Hammond 2019). Test-retest reliability with healthy subjects was reported as poor for hyoid excursion (ICC < 0.5) and slightly improved for area of submental muscles (ICC 0.62 to 0.79) the same pattern was found for intra-rater reliability ranging from ICC = 0.38 to 0.71 and inter-rater reliability ranging from ICC = 0.32 to 0.70 (Winiker, 2019). Overall, US may provide less expensive, low risk, non-invasive, repeatable assessment that patients can complete in a natural position. US provides improved clarity of structural borders of the submental muscles

compared to other techniques (Macrae et al., 2013), however this has not been evaluated in individuals with dysphagia. Ongoing refinement of measures and technical advances are required for clinical application of US as a valuable tool for swallowing assessment, treatment evaluation and biofeedback.

In summary, dysphagia diagnosis and management are only as good as the quality of available assessments. Each assessment technique has advantages and limitations as summarised in Table 3.1. A combination of behavioural and instrumental assessment techniques can increase the effectiveness in identifying patients with dysphagia. Current assessment techniques are implemented with inconsistent methodology and subjective interpretation which increases the risk of inaccurate diagnosis of underlying pathophysiology preventing appropriate treatment planning. Timely and accurate diagnosis to facilitate early targeted intervention for dysphagia is associated with reductions in the length of hospital admission, readmissions, incidence of pneumonia, health care costs and morbidity (Allen et al., 2020; Perry et al., 2019).

Table 3.1

Comparison of Swallowing Assessment Techniques

	CSE	VFSS	FEES	Mano-metry	Ultra-sound
Non-invasive procedure	✓	✓	x		✓
Does not exposure the patient to radiation	✓		✓	✓	✓
Requires specialist equipment and expertise	x	✓	✓	✓	✓
Widely used in clinical practice	✓	✓	✓	x	x
Allows for visualisation of all phases of swallowing		✓	x	x	x
Procedure can be extended for rehabilitation and assessment of fatigue	✓	x	✓	✓	✓
Direct visualisation of bolus transit during swallow	x	✓	x	x	x
Visualisation of pre-swallow aspiration/penetration	x	✓	✓	x	x
Visualisation of the extent of aspiration during swallow	x	✓	x	x	x
Visualisation of post-swallow residue	x	✓	✓	x	x
Excellent temporal resolution	x	x	✓	✓	
Visualisation of swallowing biomechanics during swallow (e.g. hyoid movement, UES opening, epiglottic deflection)	x	✓	x	x	✓*
Visualisation of muscle morphology	x	x	x	x	✓
Visualisation of secretion management, oedema and tissue integrity	x	x	✓	x	x
Visualisation of vocal fold mobility and glottic closure	x	x	✓	x	x
Assessment of sensorimotor response to the equipment, residue, or aspiration/penetration	x	x	✓	x	x
Assessment of amplitude and duration of pharyngeal pressures and UES relaxation during swallowing	x	x	x	✓	x
Validated metrics used for analysis	x	✓	✓	✓	✓

Note. Summary of clinical features / attributes of different swallowing assessment procedures. *Denotes that ultrasound allows for visualisation of some elements of biomechanics such as epiglottic deflection cannot be visualised with ultrasound.

Chapter 4. Huntington's Disease

As discussed in Chapter 2, swallowing is a complex sensorimotor task, requiring a highly coordinated sequence of activation throughout several cortical, subcortical and peripheral regions. Any disruption of this sequence or dysfunction in the neuromuscular pathways associated with deglutition can result in dysphagia (Dziewas et al., 2017a). Dysphagia is defined as the "difficulty or inability to move a bolus safely and effectively from the oral cavity to the oesophagus" (Ortega et al., 2017, p.576). Neurological disorders are the predominant cause of dysphagia (Buchholz & Robbins, 2003; Ertekin & Aydogdu, 2003; White et al., 2008). Several neurological disorders are associated with dysphagia; these include but are not limited to stroke, dementia, cerebrovascular disease, PD, cerebral palsy, intracranial lesions, multiple sclerosis, MND and Huntington's disease (HD) (Clavé & Shaker, 2015; Daniels, 2006; Dziewas et al., 2017a; Sasegbon & Hamdy, 2017). Dysphagia symptoms are amongst the most prevalent in many neurodegenerative disease; however, HD appears underrepresented in the general dysphagia literature with a notable absence from systematic reviews evaluating susceptible neurodegenerative populations (Clavé & Shaker, 2015; Keage et al., 2015; Ortega et al., 2017; Takizawa et al., 2016).

Huntington's Disease (HD) is an autosomal-dominant neurodegenerative disease characterised by a triad of impairments, including motor, cognitive, and psychiatric disturbances (Bates et al., 2015b). The disease typically manifests during the fourth decade of life and is on average fatal 10-20 years from diagnosis (Bates et al., 2015b; Ghosh & Tabrizi, 2018; Novak & Tabrizi, 2010). Prevalence of HD has increased since the advent of diagnostic genetic testing and is estimated as 10-14 per 100,000 (Baig et al., 2016; McColgan & Tabrizi, 2018).

4.1 Neurophysiology of Huntington's Disease

HD is caused by an unstable expanded cytosine-adenine-guanine (CAG) repeat sequence in exon 1 of the huntingtin gene. This expanded sequence encodes a mutant version of the huntingtin protein (*htt*), termed mutant huntingtin, which causes widespread molecular and cellular anomalies, resulting in neural and clinical deterioration (MacDonald et al., 1993; Ross et al., 2014). The *htt* protein is expressed in all mammalian cells throughout the CNS and skeletal muscles, but most commonly accumulated in the brain (Dayalu & Albin, 2015). This altered tertiary structure causes a number of molecular abnormalities which result in neuronal cell dysfunction and death causing cumulative atrophy of the basal ganglia and other cortical regions (Thu, Oorschot, Tippett, Nana, Hogg, et. al., 2010).

Normal CAG allele repeat length is < 27, intermediate range is 27 to 35 and affected range is > 36. Those with a CAG repeat of 36 to 39 are considered to have incomplete penetrance and may develop HD later in life, or not at all (Rubinsztein et al., 1996). Due to the genetic dominance, those with a CAG of 40 or more have complete penetrance and will develop HD (Dayalu & Albin, 2015; McColgan & Tabrizi, 2018; Roos, 2010). Longer CAG repeats generally correlate to earlier symptom onset and faster disease progression as demonstrated in cases of Juvenile HD with typical CAG repeats > 55 (Bates et al., 2015b; Dayalu & Albin, 2015; Roos, 2010). Despite the clear genetic cause of HD, there are significant variations in genotype and phenotype (The et al., 2004).

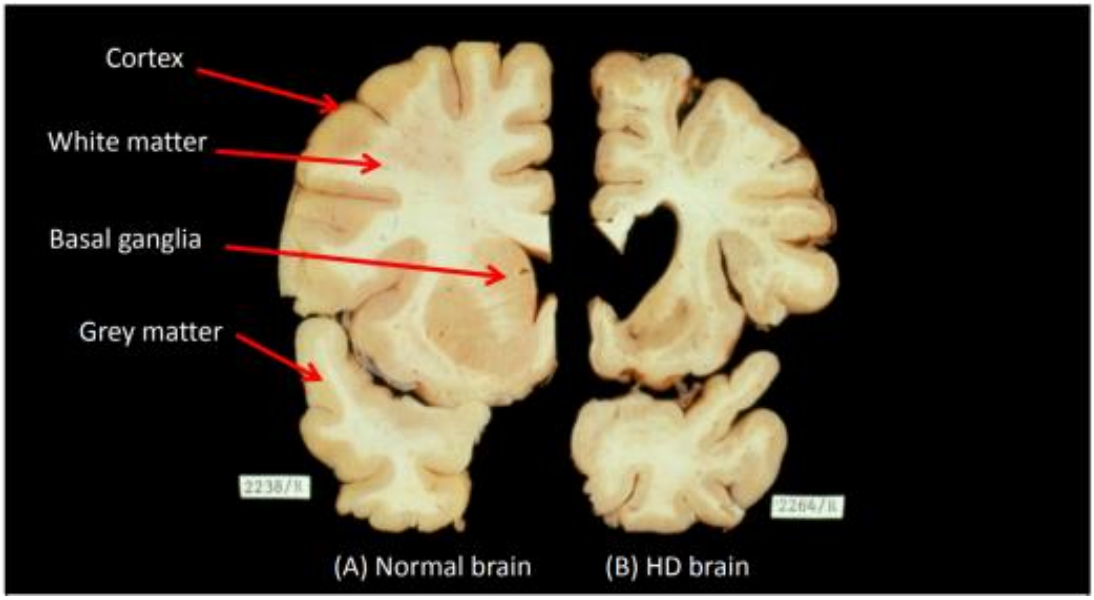
4.1.1 Basal Ganglia and Cortical Pathology

Degeneration of the basal ganglia circuits are associated with the most prevalent movement disorders such as PD and HD (Pavese & Brooks, 2013). The basal ganglia are a group of highly interconnected grey matter structures consisting of the striatum, subthalamus and substantia

nigra. Deterioration of the striatum is the first and most prominent neurophysiological characteristic of HD (Estevez-Fraga et al., 2021), as demonstrated in Figure 4.1 (Albin, 1995).

Figure 4.1

Cross-sectional Area of the Forebrain: Comparison of a Normal Brain and an HD Brain



Note. This image demonstrates significant atrophy of the basal ganglia and diffuse reduction in cortical volume in the HD affected brain. From Huntington's disease: Understanding a mutation. (2011) by Bay, J., Graves, A., Mora, H., Dragunow, M., Narayan, P., & Faull, R. LENScience Connect Senior Biology Seminar Series. Retrieved 1st September 2017, from https://www.lenscience.auckland.ac.nz /en/about/teaching-and-learning-resources/senior-biology-learning-resources/ huntingtons-disease-understanding-a-mutation/what-is-huntingtons-disease.html

Several studies have reported significantly reduced bilateral volume of the striatum and associated cortical regions before manifestation of signs (Dayalu & Albin, 2015; Dominguez et al., 2016; Estevez-Fraga et al., 2021). The basal ganglia have extensive connections to the

cerebral cortex, thalamus and subcortical nuclei (including the brainstem nuclei) (Pavese & Brooks, 2013). The basal ganglia nuclei are involved in a variety of functions to facilitate, inhibit and control movements through modulation of the direct and indirect motor pathways (Bashir & Jankovic, 2018). As previously described in Chapter 2 (p. 36), basal ganglia dysfunction is associated with a high incidence of dysphagia (Suntrup et al., 2012; Wilmskoetter et al., 2020). Deglutition is an example of one such physiological function requiring basal ganglia modulation as part of the direct and indirect motor pathways. In HD, reduced activation of the indirect motor pathway, which attenuates and inhibits movements, results in loss of thalamo-cortical output which causes hyperkinetic choreic movements (Feinstein & Walker, 2018). In addition, the loss of striatal neurones within the direct motor pathway which facilitates voluntary movement results in hypokinetic movements (McColgan & Tabrizi, 2018). Further, the cortico-striatal neuronal deterioration impacts integration of afferent feedback between the motor cortex and adjacent cortical and subcortical regions (Bhatnagar, 2013; Waldvogel et al., 2014). This results in impairments of control, inhibition, and regulation of voluntary movements.

Longitudinal imaging studies have identified degeneration of white matter microstructure in premanifest HD affecting sensorimotor regions and longer corticostriatal connections associated with observed clinical outcomes occurring first (Estevez-Fraga et al., 2021; McColgan et al., 2017). Over the disease progression, gross neuronal loss and widespread atrophy or thinning of the white matter neocortex and basal ganglia has been observed in HD (Dayalu & Albin, 2015; Dominguez et al., 2016; Thu et al., 2010). In manifest HD, an average of 30% neuronal loss of the prefrontal cortex and 40% to 55% neuronal loss of the motor cortex has been identified (Soloveva et al., 2018). These neuropathological changes therefore

contribute to the onset of dysphagia as several of these cortical regions are activated during swallowing as previously described in Chapter 2.

4.2 Symptom manifestation in HD

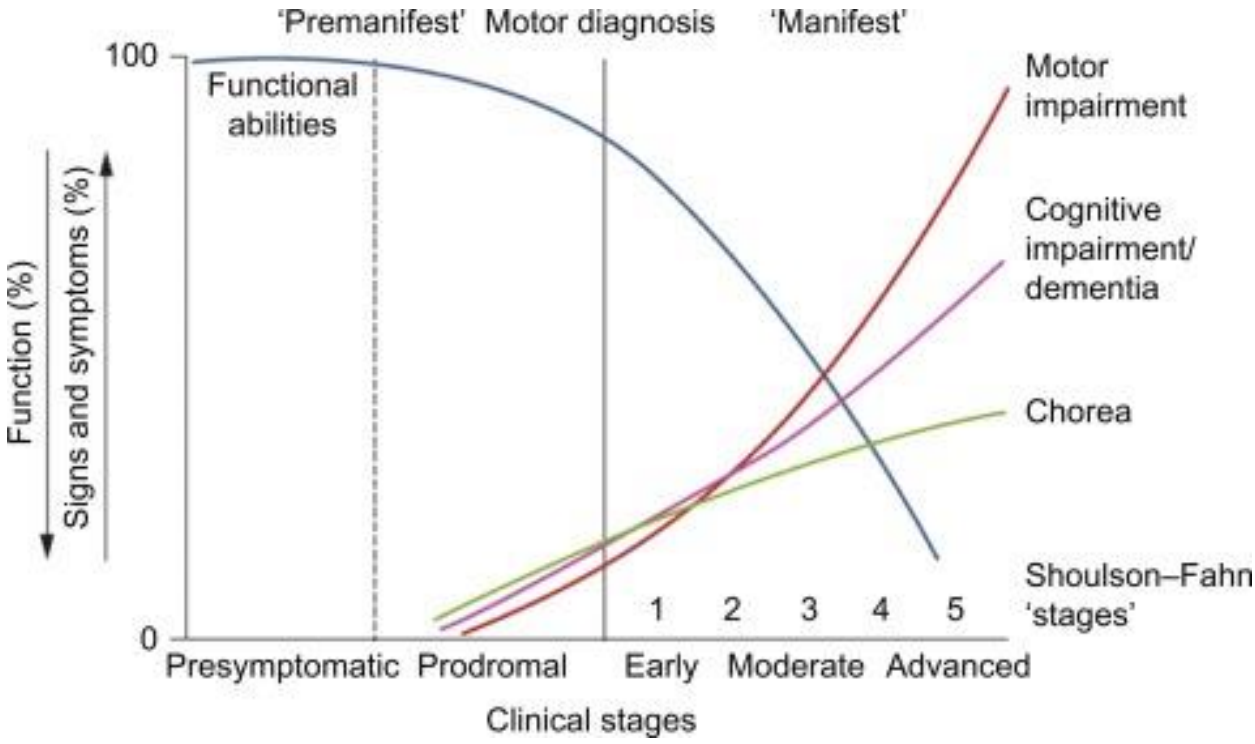
Diagnosis is confirmed with genetic testing, family history and presence of atypical movements as measured by an expert rater using the clinical Unified Huntington's Disease Rating Scale (UHDRS) total motor score diagnostic confidence score (Huntington's Study Group; Kremer, 1996; McColgan & Tabrizi, 2018; Reilmann et al., 2014; Ross et al., 2014).The UHDRS includes subjective ratings of four domains: motor function, cognitive function, abnormal behaviour and functional capacity; however, highly prevalent symptoms such as dysphagia are notably missing. The UHDRS is heavily dependent on rating of motor symptoms which may limit the clinical utility in patients with primarily cognitive symptoms. The total functional capacity score obtained via the UHDRS corresponds to the five stage Shoulson-Fahn Rating Scale. This subjective scale ranging from early to late stage HD is based on judgements of brief statements to characterise the level of dependence required for activities of daily living (ADLs) (Shoulson & Fahn, 1979). The UHDRS and Shoulson-Fahn Rating Scale are frequently used for disease stage classification in clinical trials (Borowsky & Sampaio, 2014). The UHDRS is designed to diagnose and monitor the rate and severity of HD progression (Huntington's Study Group; Kremer, 1996); however, it is frequently used as an outcome measure in treatment studies. As the UHDRS is likely not sensitive enough to identify changes post-treatment, Borowsky and colleagues (2014) suggested that intervention studies should include specific outcome measures to evaluate changes in cognitive, mood and motor function (Borowsky & Sampaio, 2014).

4.2.1 Signs and Symptoms of HD

The stages of HD are summarised in Figure 4.2, these range from presymptomatic to advanced or late stage HD. Symptoms eventually progress resulting in a total loss of independence and individuals with late stage HD typically require 24 hour nursing care (McColgan & Tabrizi, 2018). Cognitive dysfunction has been reported in premanifest HD through neuropsychological testing compared to healthy controls (Paulsen et al., 2014; Tabrizi et al., 2013). There are significant changes in verbal learning, attention, memory recall, motor planning, dual-tasking, sensory perception and processing prior to motor symptom onset (Harrington et al., 2014; Misiura et al., 2017; Paulsen et al., 2014; Paulsen et al., 2017; Reyes et al., 2021; Wild & Tabrizi, 2014). Specifically, changes in the Symbol Digit Modalities Test and Stroop Word Reading test are sensitive measures of cognition associated with different stages of premanifest and manifest HD (Estevez-Fraga et al., 2021; Tabrizi et al., 2013). This pattern of neurocognitive decline in premanifest and manifest HD has been reported to correlate with caudate atrophy (Dominguez et al., 2016). Non-motor skill learning is relatively unaffected in HD, however, increased cortical recruitment is required for attention, processing and organisation due to fronto-striatal pathway dysfunction (Pillon et al., 1993; Quinn et al., 2001). Impairments in motor skill learning, specifically new sequences, are evident in HD, but the ability to learn new motor mappings with integration of perceptual cues is spared (Gabrieli et al., 1997; Willingham et al., 1996). Behavioural or neuropsychiatric changes are also observed in all stages of HD (Roos, 2010). Depression, anxiety, apathy, irritability and obsessive-compulsive behaviours are the most common disorders reported in HD (Dayalu & Albin, 2015; McColgan & Tabrizi, 2018). Preliminary imaging studies have identified significant correlations between apathy scores and disturbance in corticostriatal connectivity (De Paepe et al., 2019).

Figure 4.2

Graphic Representation of the Clinical Stages and Associated Symptoms of Huntington's Disease



Note. Summary of the clinical stages of Huntington's disease (x-axis), the associated functional capacity and common symptoms on the y-axis. Reprinted with permission from: "Huntington disease" by Ghosh, R., & Tabrizi, S. J. (2018). *Handbook of Clinical Neurology, 147*, 255-278.

Motor impairments in HD impact on both voluntary and involuntary movements (Novak & Tabrizi, 2010). Hyperkinetic disorders are prominent and the most recognisable symptom in early HD characterised by involuntary choreic movements, impaired tandem gait, dysdiadochokinesis and instability in standing or walking (Bilney et al., 2003a; McColgan & Tabrizi, 2018; Reilmann et al., 2014; Reyes et al., 2018; Ross et al., 2014). Irregular, rapid and

unpredictable involuntary movements of the face and upper limbs are most common (Roos, 2010). These hyperkinetic movements are often exacerbated by stress, fatigue, acute illness or anxiety (Novak & Tabrizi, 2010). Impairment of voluntary movement is more functionally disabling than chorea (Wild & Tabrizi, 2014), with impaired coordination or sequencing of rapidly altering movements (Quinn et al., 2001). As the disease progresses, increased rigidity, akinesia, hypokinesia and dystonia are more common (Dayalu & Albin, 2015; Reilmann et al., 2014). Hypokinesia is universal in late stage HD, characterised by slow initiation and execution of movements (Louis et al., 1999; Roos, 2014). Dystonia or increased muscle tone is highly prevalent and leads to sustained involuntary contraction of the cervical neck musculature, shoulder rotation and trunk flexion (Roos, 2014). Bradykinesia in HD is not simply a slowness of movement, certain aspects of tasks take longer related to sequence complexity and accuracy demands (Gabrieli et al., 1997). Sensory processing and cortical demands impact on regulation of motor output, such that smoother transitions are evident in simple and well-learnt motor tasks (Lo et al., 2020; Purcell et al., 2019; Quinn et al., 2001). Deficits in postural stability and motor control have been identified in premanifest HD and manifest HD consistent with increased proprioceptive and cognitive task demands (Panzera et al., 2011; Porciuncula et al., 2020). The observed irregular and imprecise amplitude of motor programs are not related to manifest disease stage (Gordon et al., 2000; Quinn et al., 2001), however, in premanifest HD, reduced precision of motor performance was significantly correlated to individuals closer to diagnosis compared to healthy controls (Rao et al., 2014).

4.2.2 Signs and Symptoms of Swallowing Dysfunction in HD

Impairments of deglutition and motor speech are inevitable as this gradual deterioration of motor control involves musculature of deglutition, speech and respiration (Chan et al., 2019; Kagel & Leopold, 1992; Pizzorni et al., 2020; Rusz et al., 2014). Corticobulbar symptoms at

any stage of HD can reveal coexistence of these mixed hyperkinetic and hypokinetic motor impairments (Kagel & Leopold, 1992).

4.2.2.1 Prevalence of Dysphagia in HD

Due to the pattern of impairment in HD and the diffuse decline of several cortical and subcortical regions, swallowing dysfunction has been suggested as a universal symptom (Kagel & Leopold, 1992; Schindler et al., 2020; Wild & Tabrizi, 2014). Mortality rates are reported to be as high as 59 - 66% following aspiration pneumonia or choking secondary to dysphagia in HD (Heemskerk & Roos, 2012; Lanska et al., 1988; Rodrigues et al., 2017; Roos, 2010; Solberg, 2018). Reported prevalence of dysphagia in HD varies across studies, dependent on methodology for selection of patients and assessment type. A review of the literature reveals between 35% and 100% of individuals with manifest HD have identified signs or symptoms of swallowing impairment (de Tommaso et al., 2015; Heemskerk et al., 2015; Keage et al., 2020; Mariscal et al., 2014; Schindler et al., 2020). Two recent studies have evaluated swallowing in patients with manifest HD using instrumental assessment techniques. Firstly, Schindler and colleagues (2020) completed FEES in a sample of 61 patients at various stages of HD. Examinations were rated by two experienced clinicians blinded to the participants' clinical history. Swallowing dysfunction was observed in 35% of early stage, 94% of moderate stage and 100% of late stage HD. The high prevalence reported in this study may be magnified by use of the Dysphagia Outcome and Severity Scale (DOSS) to rate the presence of dysphagia. This scale includes subjective judgements such as independence during mealtimes, and do not capture the prevalence of dysfunctional swallowing biomechanics at each stage of HD. Similarly, Keage and colleagues (2020) reported oral and pharyngeal dysphagia in 77.6% (n = 49) of participants (Keage et al., 2020); however, all individuals in this study were referred for VFSS due to overt signs of dysphagia introducing a selection bias.

VFSS and FEES have been increasingly utilised for assessment of swallowing in HD over the last ten years (Pizzorni et al., 2020). These instrumental examinations are described as 'feasible' in the diagnosis of dysphagia in patients with HD, but Pizzoni and colleagues (2020) noted that the reliability and measurement accuracy of instrumental assessment methods has not been evaluated in HD. The European Huntington's Disease Network recommend imaging for assessment of swallowing in HD as objective clinical measures, such as the TWST, were not sensitive enough to identify impairment compared to FEES (Pizzorni et al., 2020; Schradt et al., 2014). Despite the increased use of instrumental assessments reported in recent research, this has not translated to clinical practise (Pizzorni et al., 2020). There remain assumptions that VFSS and FEES are not practical for HD patients due to hyperkinetic motor symptoms and postural difficulties (de Tommaso et al., 2015).

4.2.2.2 Swallowing Related Quality of Life

The negative impact of dysphagia on QoL, participation and disease burden has been well documented in other neurological and degenerative conditions such as PD, Alzheimer's disease, Multiple Sclerosis and Friedreich's ataxia (Ekberg et al., 2002; Leow et al., 2010; Vogel et al., 2014). Mild or subtle dysphagic symptoms can have significant effects on psychosocial wellbeing of individuals with PD and their families (Miller et al., 2006). In HD, the complex contribution of cognitive impairment, behavioural dysfunction with altered motor control can significantly impact the individual's perception of their dysphagic symptoms (Wild & Tabrizi, 2014). Dysphagia is associated with reduced QoL and increased caregiver burden in HD (Cubo et al., 2015; Mariscal et al., 2014). Additionally, recognition of the onset of swallowing symptoms can be very difficult for individuals with HD, particularly those who have previously witnessed swallowing decline of a relative or have a carer's perspective of

dysphagia consequences (Heemskerk & Roos, 2011). People may be hyper-concerned and frightened by swallowing decline which can negatively impact QoL (Aziz et al., 2010; Hamilton et al., 2012). Many may have poor insight or deny issues and refuse referral to Speech and Language Therapy (SLT) for swallowing management. In these cases additional focus on education and counselling is required (Hamilton et al., 2012; Kagel & Leopold, 1992; Stewart, 2012). Malnutrition and weight loss are commonly associated with both HD and swallowing related QoL (Heemskerk et al., 2014; Heemskerk et al., 2015). Despite higher than average caloric intake, weight loss is correlated with rate of disease progression and higher CAG repeats (Aziz et al., 2008; Roos, 2014). This sign is influenced by several variables including metabolic dysfunction, changes in appetite, self-feeding difficulties, impaired mastication and presence of dysphagia (Dayalu & Albin, 2015; Trejo et al., 2004).

As the triad of contributing factors in HD are unique, disease specific QoL measures have been developed for patient reported outcomes. These include the Huntington's Disease Dysphagia Scale (Heemskerk et al., 2014) and The Huntington's Disease Health-Related Quality of Life questionnaire (HDQLIFE) which have been developed to identify dysphagic symptoms and evaluate the impact of speech and swallowing changes on QoL (Carlozzi et al., 2016). Neither of these HD specific questionnaires have been validated against instrumental assessment. These HD tools have not yet translated to routine clinical practice and other questionnaires such as the SWAL-QoL have been most commonly used as a swallowing QoL outcome measure in HD research (Manor et al., 2018; Reyes et al., 2015; Schradt et al., 2018; Schradt et al., 2016). A systematic review of dysphagia specific QoL tools described the SWAL-QoL as the most reliable and valid measure of swallowing related QoL in neurological disorders covering all World Health Organisation International Classification of Function, Disability and Health areas (Keage et al., 2015).

4.2.2.3 Correlation of Disease Pathology and Dysphagia

Despite the high prevalence of dysphagia in HD and serious consequences associated with this symptom, the progression and understanding of swallowing dysfunction is relatively unknown (Pizzorni et al., 2020). Two systematic reviews have evaluated the literature of dysphagia in HD. The first by Heemskerk and Roos (2011) found five studies published between 1985 and 2009 which described swallowing in HD (two of which were single case reports). The second systematic review included 24 studies evaluating swallowing in HD between 2009 and 2018; only ten of these were articles published in peer-reviewed journals. The authors acknowledge the cautious inclusion of grey literature in order to present all available and relevant information in this limited field of research (Pizzorni et al., 2020).

Sparse literature exists using instrumental swallowing assessments to characterise HD biomechanics. A recent study identified a strong correlation ($p < 0.001$) between severity of dysphagia and disease progression (Schindler et al., 2020). A sample of 61 participants with manifest HD at various disease stages and 31 healthy control subjects underwent FEES. It was not stipulated if this patient cohort were randomly selected or identified due to swallowing concerns. Participants completed three trials of liquid, semisolid and solid boluses. Each swallowing trial was rated using the PAS to quantify swallowing safety and the five-point Yale Pharyngeal Residue Severity Rating Scale to judge the severity of post-swallow pharyngeal residual. Dysphagia severity was rated using the Dysphagia Outcome and Severity Scale (DOSS) based on level of nutrition, diet modification, independence and functional observations (O'Neil et al., 1999). Although these measures provided quantifiable data, results were obtained via ratings which were based largely on subjective judgements such as strength of cough. This study did not include any objective measurements of timing or swallowing

biomechanics. The two raters were blinded to the disease stage of participants, but the inter-rater agreement was not specified. In addition, the worst ratings of swallowing safety and efficiency for each participant were selected for statistical analysis; therefore, the frequency of swallowing trials with airway invasion or residual according to bolus type was not specified. This study reported that motor impairment as quantified by the UHDRS total motor score could be a predictive factor to identify those at risk of dysphagia. It would be beneficial to further explore this correlation with objective measurements of swallowing biomechanics. Quantification of the amount of post-swallow pharyngeal residual observed at each disease stage was not provided. Dysphagia severity and PAS significantly worsened with disease progression ($p < 0.001$); however, as previously highlighted, the reported 100% prevalence of severe dysphagia in late stage HD was classified using subjective judgements as part of the DOSS.

Another study retrospectively described the clinical characteristics of 49 individuals with HD using VFSS and clinical examination (Keage et al., 2020). VFSS were repeated in seven cases at highly variable time points, a mean of 652.57 days (SD 347.75, range 231 - 1115 days) after the initial assessment. The repeated VFSS also differed in terms of protocols and equipment (e.g. frames per second) which limited retrospective comparison. No timing or displacement measures were obtained from VFSS data, instead the Bethlehem Assessment Scale and PAS were used. The Bethlehem Assessment Scale is a standardised clinical tool in which 10 anatomical swallowing domains are rated during VFSS using a four-point scale. Three bolus types were assessed during VFSS (thin fluids, puree and muffin textures), the protocol for each participant such as the number of trials of each texture was not stated. This study identified a diverse pattern of dysphagic symptoms across all disease stages; these findings are discussed below and summarised in Table 4.1. The repeated assessments indicated high individual

variability; therefore, no systematic progression of dysphagia could be identified in this cohort (Keage et al., 2020). Kagel and Leopold (1992) also evaluated swallowing across disease stages with VFSS and clinical evaluation. They reported increased rigidity and parkinsonism symptoms associated with late stage HD but did not specify the protocol and did not include any re-assessments as part of this longitudinal study. The authors report hyperkinetic or hypokinetic dysphagia sub-groups across all stages of the disease. The key characteristics observed across bolus types and volumes are summarised in Table 4.1. Other studies using non-instrumental assessments have reported significant correlations between dysphagia severity and CAG repeat, age, disease duration or motor impairment (de Tommaso et al., 2015; Mariscal et al., 2014). These studies utilised clinical dysphagia screening tools such as the EAT-10 and clinical observations were rated using the DOSS. These studies were not blinded and did not include any instrumental measures of swallowing biomechanics.

The presence of swallowing dysfunction as an early symptom of the disease has further been evidenced in two preliminary MRI studies. Both of these studies represent grey literature from conference proceedings, however, were deemed relevant for inclusion in this literature review. Michou et al. (2017) reported deactivation of the frontal cortex at rest and during swallowing tasks in early HD with associated mild dysphagic symptoms compared to healthy controls. In addition, increased activation of the precentral cortex and anterior cingulate gyrus was reported. Another study identified atrophy of the cortical regions associated with deglutition in patients with moderate or severe dysphagia and HD, not related to disease stage (Schumann et al., 2018). Interestingly, atrophy in known regions of periodic deterioration in HD such as the striatum and thalamus were not significantly different from those HD patients with no or mild dysphagia (Schumann et al., 2018).

The stability of dysphagic symptoms across the stages of the disease is unclear, some studies report limited detectable deterioration between early and mid-stages, and significant changes associated with late stage disease (Monaco et al., 2014; Schindler et al., 2020), whilst others report wide variability with no detectable pattern of decline (Keage et al., 2020). Pizzorni et al. (2020) summarised clinical markers associated with risk of dysphagia in HD as high UHDRS motor score, cognitive impairment, dysphonia, dysarthria, impaired lingual movement and old age. More longitudinal studies with clear methodologies and objective outcome measures are required to identify the evolution of swallowing decline across disease stages and investigate the pattern of variability in HD. This will aid understanding of dysphagia progression and ensure targeted intervention (Keage et al., 2020).

4.2.3 Pre-oral Phase Dysfunction

Identified characteristics of dysphagia in HD are summarised in Table 4.1 below. Firstly, even in the absence of overt motor symptoms, cognitive and behavioural dysfunction alone may be sufficient to induce pre-oral dysfunction. Patients with diffuse cortical dysfunction may exhibit potentially dangerous mealtime behaviours which compromise the swallowing safety despite relatively intact oropharyngeal swallowing function as measured during controlled assessment (Leopold & Kagel, 1997). Tachyphagia and overfilling the oral cavity has been described in other basal ganglia diseases such as PD and progressive supranuclear palsy associated with rigid or bradykinetic motor symptoms resulting in slow and hesitant mastication (Leopold & Kagel, 1996). The rate of ingestion is influenced by many factors such as cultural norms, emotional state, psychosocial factors, in addition to oral sensory feedback regarding the temperature taste, palatability and bolus volume (Leopold & Kagel, 1997; Perlman & Christensen, 2003). In HD, tachyphagia is the most commonly reported symptom associated with both hyperkinetic disinhibited movements and hypokinetic movements with reduced oral

control and bolus manipulation (Kagel & Leopold, 1992; Pizzorni et al., 2020). Self-feeding is immediately observed as excessively rapid in HD combined with disorganised and irregular mastication. Tachyphagia is frequently reported with coughing and choking episodes which infers an increased risk of aspiration and asphyxiation (Leopold & Kagel, 1997). Kagel and Leopold (1992) reported 30.6% of patients with HD (n = 39) required supervision and assistance at mealtimes due to reduced self-feeding efficiency, impulsivity and inability to self-monitor bolus size or pace of eating.

Irritability and apathy can impair eating and drinking, with reduced initiation and motivation to eat or maintain good oral hygiene (Hunt & Walker, 1989; Kagel & Leopold, 1992). Poor oral hygiene, reduced attention, inability to self-feed, reflux disorder, medications and reduced mobility often magnify minor dysphagic symptoms (Hamakawa et al., 2004; Heemskerk & Roos, 2011) and increase the risk of aspiration pneumonia (Langmore et al., 1998).

Table 4.1

Summary of Ingestive Swallowing Dysfunction Characteristics in Huntington's Disease

Sign or symptom of dysfunctional deglutition	Implied biomechanical impairment	Implied pathophysiology	Reported by
Pre-oral phase: • Tachyphagia (rapid eating) • Reduced inhibition and insight into volume and pace of oral intake • Impulsive eating • Increased appetite • Overfilling oral cavity • Halitosis • Hypoactive or hyperactive gag reflex • Involuntary abrupt movements of limbs, head, neck and face • Reduced hand to mouth self-feeding ability • Postural instability • Hyperextension of the head and trunk • Xerostomia • Increased sialorrhea • Impaired smell identification	• Hyperkinetic choreic limb movement, • Cervical dystonia • Hypokinetic motor impairment • Cognitive impairment • Behavioural changes • Executive function impaired • Reduced inhibition from basal ganglia and subsequent uninhibited cortical modulation • Increased appetite part of metabolic dysfunction and impact of hyperkinetic disorder • Altered sensorimotor function of the glossopharyngeal nerve (CN IX) • Medication induced xerostomia • Unclear if increased saliva production or reduced oral sensory awareness • Olfactory processing impairment	Cortico-striatal dysfunction, depletion of GABA neurotransmitter, disruption of the basal ganglia sensorimotor pathways. Disruption of afferent input and cortical modulation of CPG.	Leopold & Kagel, 1985; Kagel et al., 1992; Hunt & Walker, 1989; Hamakawa et al., 2004; Lee et al., 2012; Wood et al., 2008; Andrich et al., 2009; Heemskerk & Roos, 2011; Pizzorni et al., 2020
Oral phase: • Reduced mandibular range of movement • Rapid and inadequate mastication • Rapid transfer of bolus • Premature spillage • Rapid and unpredictable lingual movements • Impaired bolus formation • Segmented or delayed lingual transfer	• Hypokinetic, rigid or bradykinetic muscles of mastication • Hyperkinetic, hypertonic, spasticity of muscles of mastication • Oral apraxia • Lingual chorea • Altered sensorimotor function of the trigeminal nerve (CN V), facial nerve (CN	Cortico-striatal dysfunction, depletion of GABA neurotransmitter, disruption of the basal ganglia sensorimotor pathways.	Leopold & Kagel, 1985; Kagel et al., 1992; Hamakawa et al., 2004; Mochizuki et al., 1999; Roos, 2010;

• Impaired control of bolus • Anterior oral spillage • Decreased / ineffective mastication • Tongue protrusion / tongue thrust • Oral residue • Lingual searching • Buccolingual chorea • Premature liquid transfer • Decreased base of tongue to posterior pharyngeal wall • Incomplete velopharyngeal approximation and nasal redirection • Dysarthria* (hypertonic/spastic) • Hypernasality*	VII), glossopharyngeal nerve (CN IX) and motor efferents of the hypoglossal nerve (CN XII) • Reduced coordination of oral phase sequence	Disruption of afferent input and cortical modulation of CPG. Altered motor program from central to peripheral control. Abnormal innervation of sensory thresholds to initiate timely motor program for pharyngeal phase.	Heemskerk & Roos, 2011; Roos, 2014; Manor et al., 2016 & 2018; Reyes et al., 2014; Keage et al., 2020; Schindler et al., 2020.
Pharyngeal phase: • Decreased oral transit time • Coughing during/after swallowing • Choking on solid food • Aspiration and penetration • Repetitive swallows • Reduced anterior hyoid excursion • Incomplete epiglottic deflection • Extended laryngeal elevation • Difficulty with laryngeal descent • Excessive eructation (belching) • Aerophagia (swallowing excessive air) • Audible swallowing • Phonation during swallowing • Pharyngeal stasis • Inhalation during swallowing	• Hyperkinetic, involuntary chorea movements of pharyngeal and laryngeal muscles • Hypokinetic, rigidity and bradykinesia of muscles of the aerodigestive tract • Impaired swallow initiation during both voluntary and involuntary swallowing • Imprecise and uncoordinated sequence of sensorimotor events • Impaired respiration and swallowing coordination • Involuntary respiratory movements • Altered sensorimotor function of the trigeminal nerve (CN V), facial nerve (CN VII), glossopharyngeal nerve (CN IX), vagus nerve (CN X) and motor efferents of the hypoglossal nerve (CN XII)	Cortico-striatal dysfunction, depletion of GABA neurotransmitter, disruption of the basal ganglia sensorimotor pathways. Disruption of afferent input and cortical modulation of CPG. Altered motor program from central to peripheral control (e.g. ‘difficult laryngeal descent’)	Leopold & Kagel, 1985; Kagel et al., 1992; Hunt & Walker, 1989; Hamakawa et al., 2004; Lee et al., 2012; Mochizuki et al., 1999; Yorkston et al., 2004; Aziz et al., 2010;

• Involuntary sniffing or grunting • Chorea of respiratory muscles • Laryngeal chorea with abrupt adduction / abduction of vocal folds during swallowing • Post-swallow residue in vallecula and pyriform sinus • Wet voice quality • Supra-cricopharyngeal residual • Cricopharyngeal dysfunction • Involuntary prosody / loudness variation* • Inhalation phonation* • Dysphonia*	• Assumed reduced pharyngeal contraction or motility, reduced hyoid movement, incomplete epiglottic deflection results in impaired UES opening	Abnormal innervation of sensory thresholds to initiate timely motor program for pharyngeal phase and oesophageal phase.	Keage et al., 2020; Heemskerk et al., 2015; Schradt et al., 2016; Manor et al., 2018; Pizzorni et al., 2020; Schumann et al., 2018; Sussmuth et al., 2012; Trender-Gerhard et al., 2016; Schindler et al., 2020;
Oesophageal phase: • Vomiting / regurgitation • Reduced oesophageal transit time • Early satiety • Impaired oesophageal emptying • High pressure and incomplete opening of lower oesophageal sphincter • Oesophageal dysmotility • Reflux • Reverse peristalsis • Hiatal hernia	• Hyperkinetic movements impacting on posture • Hypokinetic, rigidity or bradykinesia of the upper oesophagus • Chorea of the diaphragm • Spasmodic contraction of the mid oesophagus	Cortico-striatal dysfunction, disruption of the basal ganglia sensorimotor pathways. Altered excitation and inhibition of pharyngeal and oesophageal phases of swallowing from CPG motor program	Leopold & Kagel, 1985; Kagel et al., 1992; Hunt & Walker, 1989; Lee et al., 2012; Andrich et al., 2009.

Note. Signs and symptoms of swallowing dysfunction. * indicates dysarthric symptoms relevant to swallowing function.

4.2.4 Oral Phase Dysfunction

A wide range of oral phase impairments have been reported in individuals with HD as summarised in Table 4.1. These abnormal behaviours are apparent during clinical observations, do not require instrumental visualisation and are likely to be influenced by a combination of motor and sensory dysfunction within the corticobulbar pathways (Steele & Miller, 2010). Involuntary and irregular tics or choreic movements of the head, neck and facial muscles particularly effect the oral phase of deglutition (Hamakawa et al., 2004; Lee et al., 2012; Roos, 2010). In contrast, hypokinetic movements of the oral musculature severely impacts on efficiency and safety of the oral phase (Heemskerk & Roos, 2011; Schindler et al., 2020).

In both hyperkinetic and hypokinetic disorders, tongue protrusion has been reported (Kagel & Leopold, 1992) and becomes increasingly impaired as HD progresses (Roos, 2014). Impaired lingual movement and protrusion was highly correlated with PAS score > 2 (sensitivity of > 86%) as visualised on FEES (Schradt et al., 2016). Oral spillage is reported due to reduced coordination and inadequate labial seal (Kagel & Leopold, 1992). Keage and colleagues (2020) reported severe lingual dysfunction in 48.6% of patients and impaired mastication in 43.9% of patients across all stages of the disease. Subjective judgement of impaired lingual control and coordination is associated with reduced efficiency in forming a cohesive bolus, poor coordination of bolus transfer resulting in premature transfer with liquids and segmented transfer with solids (Heemskerk & Roos, 2011; Kagel & Leopold, 1992; Keage et al., 2020; Schindler et al., 2020). Poor oral clearance and voluntary initiation of swallowing results in oral residue with more solid textures (Keage et al., 2020). Poor oral coordination and control combined with tachyphagia leads to large pieces of insufficiently masticated food being swallowed which increases the risk of choking and risk of death by asphyxiation (Heemskerk & Roos, 2011; Kagel & Leopold, 1992; Leopold & Kagel, 1985).

There is no evidence that reduced oral control and spillage is due to muscle weakness in HD. Oral motor examination reported reduced diadochokinetic rates compared to normative range associated with incoordination in HD (Manor et al., 2016), but mandibular function is reportedly stable over time (Keage et al., 2020). Reyes et al. (2014) also measured submental muscle activity of HD patients with sEMG during saliva and water swallowing as well as expiratory muscle training tasks. There was no significant difference between the muscle activity of HD patients compared to healthy controls during swallowing and low resistance expiratory muscle tasks (25% resistance), decreased muscle activity was only apparent when increased effort was required with a resistance of 75% (Reyes et al., 2014).

Keage et al. (2020) and Kagel and Leopold (1992) reported impaired sensory responses such as altered lingual tactile discrimination and lack of adaptation of swallowing biomechanics to different bolus volumes in HD. These abnormal ataxic-type behaviours may be reflective of errors in the sensorimotor afferent loops from peripheral oral cavity which impacts the cortical modulation and subsequent regulation of the motor response (Kagel & Leopold, 1992). Sensorimotor swallowing dysfunction in HD has been characterised by incoordination between oral and pharyngeal swallowing events observed on FEES (Schindler et al., 2020). This disturbance of muscle coordination and segmented unsmooth sequencing in HD has been termed ‘oropharyngeal dyssynergia’ (Manor et al., 2018).

4.2.5 Pharyngeal Phase Dysfunction

Impairments of almost every aspect of the pharyngeal phase of swallowing have been reported across the literature as summarised in Table 4.1. Pre-oral spillage and pharyngeal delay are frequently reported in HD, but all reports are based on subjective judgements of when normal swallowing should be initiated. On VFSS examination, Keage and colleagues (2020) reported

significantly delayed pharyngeal swallowing initiation in all participants (n = 49) with thin fluids, in 85.1% with a puree bolus and 82.9% with a muffin. The severity of this delay was judged by a clinician using a standardised rating scale, and all bolus consistencies reportedly reached the level of the valleculae before swallowing was initiated. The extent of delayed pharyngeal initiation significantly correlated with disease duration and the site of the bolus head at the point of initiation was more proximal as disease burden increased ($p < 0.05$) (Keage et al., 2020). Heemskerk et al. (2015) reported pre-swallow spilling in up to 45.2% of patients (n = 45) with a 10 ml liquid bolus. An endoscopic evaluation of swallowing in HD patients (n = 86) reported pre-swallow spillage correlated with higher PAS scores across all consistencies; in addition, pre-swallow spillage was associated with other sensorimotor impairments such as dysarthria, dysphonia, perceptually impaired voluntary cough initiation and cough strength judged by an unblinded rater (Schradt et al., 2016). Another study reported frequently delayed initiation of the pharyngeal phase observed on FEES, with pre-swallow spillage in 85% of patients (n = 14) and bolus reaching the vallecula in 50% of patients, as measured using a three-point scale judged by one clinician as normal to abnormal (Manor et al., 2018). The authors also reported abnormal pharyngeal phase correlated with 'weak' volitional cough as subjectively judged by one clinician. No significant difference in pre-swallow spillage across disease stages has definitively been reported in studies using instrumental evaluation of swallowing in HD (Heemskerk et al., 2015; Pizzorni et al., 2020; Schradt et al., 2016).

A frequently cited study from 1985 evaluated 12 patients with HD and dysphagia using a variety of clinical and instrumental methods (Leopold & Kagel, 1985). VFSS, pulmonary testing, endoscopy and oesophageal manometry were all utilised alongside clinical observations which included oral-motor examination. Dysphagia severity was judged by a clinician using an unweighted rating scale for all features which makes comparison between

studies problematic. Eleven patients had moderately advanced HD, one had late stage disease. On video evaluation, the authors report that poor bolus formation and propulsion of the oral phase resulted in delayed pharyngeal initiation and reduced pharyngeal stasis characterised by post-swallow pharyngeal residue at the level of the pyriform sinus. In addition to delayed pharyngeal initiation, nasal redirection was reported in two patients, impaired cricopharyngeus function was subjectively judged in two patients, five patients aspirated. The authors failed to specify frequency of aspiration or bolus type aspirated but concluded that choking was associated with attempts to swallow large unchewed bolus (Leopold & Kagel, 1985). Another study using VFSS reported delayed and incomplete velopharyngeal closure on all consistencies which significantly correlated with disease duration ($p < 0.05$) (Keage et al., 2020). Heemskerk and colleagues (2015) reviewed swallowing biomechanics in early, mid and late stage HD (n = 45), this grey literature has not been published in a peer-reviewed journal, but this is included as the only study to detail objective group VFSS timing measures with fluid and solid bolus consistencies. However, recordings were at 15 fps, which is likely insufficient for accurate timing measures of swallowing (Levine & Rubesin, 2017). The authors reported significantly shorter oral and total transit times compared to normative data across all consistencies. Kagel and Leopold (1992) also reported delayed and uncoordinated pharyngeal phase in 10 out of 30 patients as observed via VFSS examination, however no further measures of swallowing initiation were detailed.

Despite a clinical belief that penetration or aspiration only occurs in advanced stages of HD (Hamilton et al., 2012), many studies have reported penetration and aspiration across all stages of HD. Schumann and colleagues (2018) reported 80% of participants (n = 21) penetrated or aspirated on FEES. In contrast, Manor et al. (2018) reported pharyngeal residual with solid textures in 57% (n = 8) of cases, but much lower frequency of penetration and aspiration 14%

(n = 2) with FEES despite the relatively comparable group. Aspiration was observed using FEES in 10 of 23 HD patients across all disease stages with suspected dysphagia (Sussmuth et al., 2012). A study using VFSS identified increased penetration and aspiration on liquids associated with pharyngeal phase delay in early HD with mild motor symptoms (Trender-Gerhard et al., 2016). Penetration and aspiration ratings significantly increased ($p < 0.05$) with stage of disease as measured by VFSS (Heemskerk et al., 2015). Post-swallow residual at the vallecula and pyriform sinus was observed in more than half of swallows with a 10 ml liquid bolus with increased risk of aspiration ($p < 0.05$) compared to solid texture (Heemskerk et al., 2015). The authors of two studies have hypothesised that the temporal coordination of swallowing is impaired in HD (Heemskerk et al., 2015; Schindler et al., 2020). Keage and colleagues (2020) also reported penetration or aspiration with all bolus types, most common with fluids (30.6%) as observed on VFSS. Fifty-one percent of individuals had compromised airway (PAS score > 3) and 32.7% silently aspirated (PAS score of 8) on at least one consistency. However, it is not stated how many swallowing trials were completed with each bolus. Schindler and colleagues (2020) reported compromised swallowing safety across all stages of HD. FEES evaluation identified silent aspiration in 7.7% of early stage, 11.8% of moderate stage and 27.8% of late stage HD (Schindler et al., 2020). This study included multiple trials of three bolus consistencies, however, the incidence of aspiration according to bolus type was not stated. In contrast, no aspiration or penetration was noted on FEES in two case studies in early-mid stage HD, but oral spillage was noted and the authors claim laryngeal and pharyngeal sensitivity were present, as a small amount of pharyngeal residue cleared with additional swallows (Alves et al., 2016).

Delayed laryngeal descent post swallow on VFSS and involuntary movements noted whilst the larynx was at maximum displacement were described in two case studies (Hamakawa et al.,

2004; Mochizuki et al., 1999). A single case study detailed timing and displacement measures but did not state frame rate of VFSS (Hamakawa et al., 2004). Incomplete BoT to posterior pharyngeal wall approximation, reduced hyoid excursion and incomplete epiglottic deflection during swallowing were reported with subsequent residual in both vallecula and pyriform sinus. Penetration was observed with large sips due to head back postural instability and reduced orolingual control (Hamakawa et al., 2004). Another study reported uncoordinated pharyngeal response and pharyngeal residual in 27 out of 29 patients after the first swallow on VFSS (Kagel & Leopold, 1992). Residue was reported in the vallecula and pyriform sinus but was not specified by bolus type. This study also reported prolonged hyo-laryngeal excursion and swallowing latency > 4 s (Kagel & Leopold, 1992). Although coughing and choking were observed on VFSS in 16 patients, aspiration or penetration was only reported in four people, the authors hypothesise that observed abrupt and forced closure of the ventricular and true vocal folds (laryngeal chorea) appeared to redirect the bolus and "reactivate pharyngeal sensory receptors" (Kagel & Leopold, 1992, p. 113), resulting in low frequency of aspiration. The authors did not include any timing or displacement measures of VFSS; therefore, all of these observations were subjectively reported. Hypokinetic dysphagia was associated with increased aspiration of larger volumes, with assumed bradykinetic swallowing response with due to diminished sensory kinematic thresholds (Kagel & Leopold, 1992).

Diffuse pharyngeal residue has been reported with all consistencies; several authors interpreted this sign as reduced pharyngeal stripping or reduced peristalsis (Hamakawa et al., 2004; Kagel & Leopold, 1992; Keage et al., 2020; Lee et al., 2012; Leopold & Kagel, 1985). However, Manor et al. (2018) hypothesised that pharyngeal phase impairment and resultant residue is likely reduced sensory input and impaired motor response not due to muscle weakness, as only some elements of motor dysfunction were noted. In addition, several studies have reported

abnormal respiratory-swallowing coordination in HD with associated episodes of aspiration or penetration (Kagel & Leopold, 1992; Manor et al., 2018; Yorkston et al., 2004), but the biomechanics of this abnormal coordination has not been fully explored in this disease. Leopold and Kagel (1985) reported 11 of 12 patients with HD had impaired respiration as measured by pulmonary flow-loop testing and seven had abrupt expiration cessation. All patients had observed signs of impaired respiration coordination including aerophagia, irregular sniffing, inhalation and phonation (Leopold & Kagel, 1985). Resumed respiration or phonation during swallowing is more common as the disease progresses (Kagel & Leopold, 1992).

Overall, oropharyngeal phase impairments in HD have similarities to corticospinal impairments described in limb literature: delayed initiation and coordination of movements due to impaired integration and processing of sensorimotor information (Gordon et al., 2000; Quinn et al., 2001). Reported impairments such as prolonged hyolaryngeal excursion could illustrate 'overshooting' of the motor response using excessive and imprecise amplitude as described in the limb literature (Gordon et al., 2000).

4.2.6 Oesophageal Phase Dysfunction

Oesophageal phase impairments are relatively underreported and not well understood in the HD literature. Kagel and Leopold (1992) reported 11 of the 35 patients exhibited oesophageal symptoms on VFSS such as eructation and aerophagia (Kagel & Leopold, 1992). Seven patients showed evidence of gastro-oesophageal reflux (Kagel & Leopold, 1992). On VFSS, redirection of the bolus coincided with respiratory chorea and required multiple clearing swallows. The authors hypothesise that chorea of the oropharyngeal and respiratory muscles interrupted intrathoracic oesophageal mechanoreceptors reducing the efficacy of oesophageal

peristalsis and emptying. Vomiting, belching and regurgitation are commonly reported in HD (Kagel & Leopold, 1992; Leopold & Kagel, 1985). Leopold and colleagues (1985) reported five out of 12 patients with mid to late stage HD had impaired oesophageal motility as judged by a non-weighted rating scale. Seven people had diaphragmatic chorea on oesophageal manometry, five demonstrated LES dysfunction but no impairment of the UES was reported (Leopold & Kagel, 1985).

A single case study utilised HRM to evaluate a patient presenting with HD and dysphagia (Lee et al., 2012). The authors reported normal UES relaxation, normal peristaltic pharyngeal pressures, but impaired pharyngeal transit due to irregular velopharyngeal approximation, and simultaneous contraction of the hypopharyngeal regions with impaired bolus transit through the UES. Spastic oesophageal motility was characterised by irregular and simultaneous contractions in 70% of 5 ml water swallows resulting in abnormal liquid transit as noted on the impedance contour (Lee et al., 2012). As this is the only report of pharyngeal and oesophageal evaluation of an individual with HD using HRM, it is difficult to generalise these findings. However, these interesting observations require further investigation to contribute to the knowledge of dysphagia characteristics in HD. A final retrospective study evaluated patients with HD (n = 68) using endoscopic gastrostomy instrumental assessment. This study revealed high prevalence of oesophagitis (32.4%), gastritis (33.8%) and pangastritis (20.6%), these symptoms significantly correlated with disease duration ($p < 0.05$) (Andrich et al., 2009). The authors noted that only 20 patients complained of gastro pain or reflux, despite the high prevalence of these features.

4.2.7 Awareness of Dysphagia in HD

In summary, there is increased awareness and interest in the clinical significance of dysphagia in HD (Pizzorni et al., 2020). It has been highlighted as a key area of interest by the European Huntington's Disease Network, with the establishment of 'Dysphagia Standards of Care Speech and Language Therapy Working Group' in 2018. As dysphagia in HD can compromise swallowing safety and efficiency from early in the disease, there is consensus that early detection and effective intervention can help to prevent choking and respiratory complications (Hamilton et al., 2012; Heemskerk & Roos, 2011; Heemskerk et al., 2015). Due to the lack of clear clinical markers, dysphagia in HD could be assumed as a distinct neuropathological symptom which requires further investigation with consistent and objective measurement techniques (Schumann et al., 2018).

Chapter 5. Treatment Approaches in Huntington's Disease

Despite the identification of the clear genetic cause in 1993, no disease modifying treatments exist to prevent or slow the progression of HD (McColgan & Tabrizi, 2018). There have been great advances in treatment options over the last decade. These include huntingtin (*htt*) lowering therapies aimed to supress transcription of the *htt* mutant protein and neuronal regeneration studies (Robinson, 2020; Tabrizi et al., 2019; Wyant et al., 2017). A recent international review of management of HD recommended that evidence-based practice should include early intervention and a combination of both pharmacological and non-pharmacological approaches (Bachoud-Levi et al., 2019).

5.1 Pharmacological and Non-pharmacological Management

Pharmacological management of HD is most commonly reported; however, evidence to support the effectiveness of these approaches is lacking and clinical decisions are often based on expert opinion or experience (Mason & Barker, 2016; McColgan & Tabrizi, 2018; Mestre et al., 2009; Wyant et al., 2017). Commonly prescribed antipsychotic or anti-choreic drugs such as tetrabenazine can have adverse effects including increased rigidity, sedation and dysphagia (Bachoud-Levi et al., 2019; Dayalu & Albin, 2015; Wyant et al., 2017).

5.1.1 Principles of Rehabilitation in HD

There is a time in premanifest HD when cortical deterioration is apparent, but significant neuronal reorganisation and increased neuroplasticity creates compensatory networks to maintain normal function (Andrews et al., 2015; Bilney et al., 2003a; Wild & Tabrizi, 2014). Neuroplasticity or brain plasticity is defined as the ability of the nervous system to modify activity through adaption and reorganisation of synaptic connections, structure, and function in response to intrinsic or extrinsic stimuli (Mateos-Aparicio & Rodríguez-Moreno, 2019). In the

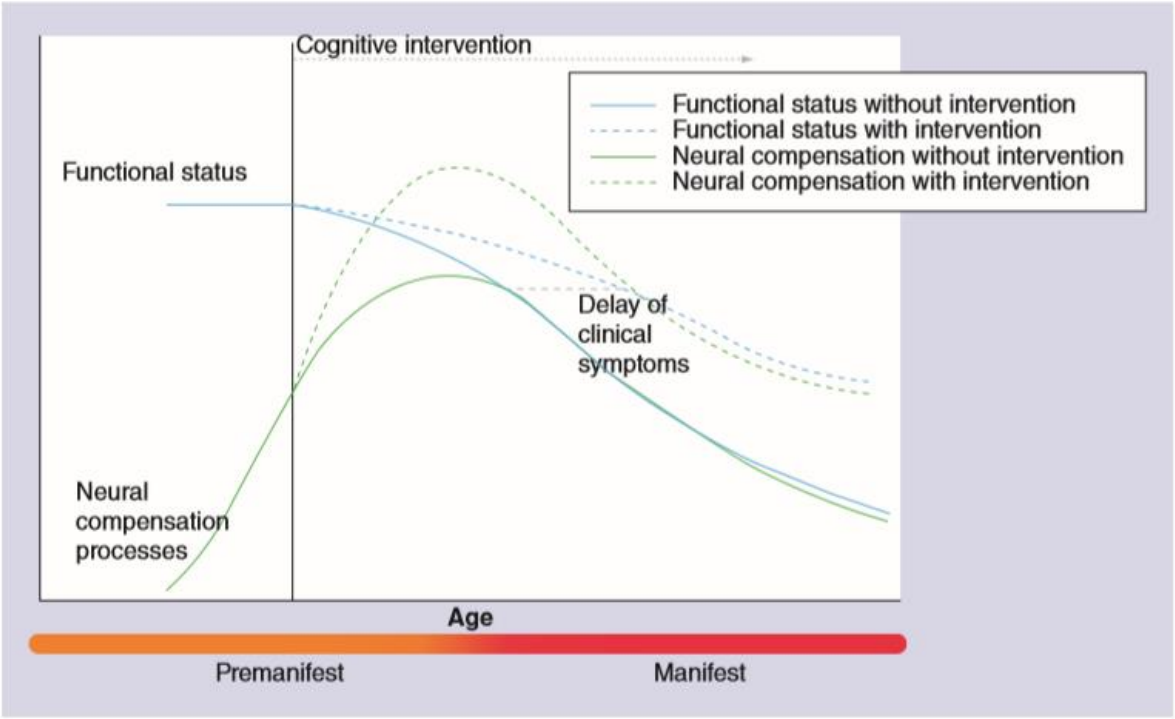
context of neurological disease or damage, neuroplasticity also refers to the brain's ability to adapt and rebuild neuronal pathways to improve or preserve function (Mateos-Aparicio & Rodríguez-Moreno, 2019). It has been hypothesised that neuroplasticity in HD results in altered neural activity in task-specific cortico-striatal pathways by recruiting additional non-task-specific cortical regions (Andrews et al., 2015; Soloveva et al., 2018). This is consistent with imaging studies that report significant deterioration in cortical and subcortical regions in the absence of functionally detectable decline in cognitive or motor tasks (Andrews et al., 2015; Poudel et al., 2015).

In recent years, there has been an increase in studies evaluating the systematic effects of rehabilitation and exercise for individuals with HD (Fritz; Petzinger; Quinn & Busse, 2017; Quinn et al., 2017; Quinn et al., 2020). A review of physiotherapy (PT) rehabilitation in PD and HD concluded that high intensity, repetitive, blocked practice with visual or verbal feedback may be the most effective rehabilitation strategy in these populations in targeting limb and trunk control as part of corticospinal intervention. Rehabilitation should focus on improving the speed and amplitude of the sequential movements for specific motor tasks (Quinn et al., 2013a). The most recent review provides clear clinical guidance to support PT intervention in HD (Quinn et al., 2020). Quinn and colleagues (2020) concluded that there is strong evidence to support PT intervention to improve fitness, motor function, and gait in persons with HD. The authors recommend that intensive task-specific rehabilitation for six to eight weeks may be beneficial for individuals with HD multiple times per year; however, the viability and financial implications of this intensive model on healthcare providers requires further consideration. Recommendations were made for further large-scale clinical trials to evaluate the effectiveness of certain aspects of PT intervention (Quinn et al., 2020).

Rehabilitation may be able to optimise the compensatory neuroplasticity present in early HD (Andrews et al., 2015; Cruickshank et al., 2015; Thompson et al., 2013). A window of opportunity has been proposed where neural reorganisation may be most amenable to intervention as represented in Figure 5.1 (Andrews et al., 2015; Bilney et al., 2003b). Early intervention may be the best preventative strategy as symptoms are mild or not evident, but degeneration in the brain is already present (Quinn & Busse, 2017; Ross & Tabrizi, 2011).

Figure 5.1

Proposed Model of Timing of Intervention to Enhance Neural Compensation and Preserve Function in HD



Note. This hypothetical model proposed by Andrews and colleagues, (2015) is specific to cognitive intervention, but can be applied to any intervention to delay clinical decline and maintain function in HD. Reprinted with permission from "Cognitive interventions to enhance neural compensation in Huntington's disease", by Andrews, S. C.,

Domínguez, J. F., Mercieca, E. C., Georgiou-Karistianis, N., & Stout, J. C., 2015, *Neurodegenerative Disease Management, 5*(2), 155-164.

Despite the neurodegenerative nature of the disease, HD may have rehabilitative potential as intervention could be implemented in premanifest gene-carriers to maintain function before symptoms appear. As impairments become more apparent, the goal of rehabilitation may not be to restore original functioning; however, task-specific rehabilitation may be 'neuroprotective' by maximising function and exploiting plasticity of neural pathways (Quinn & Busse, 2017; Quinn et al., 2013a). The consensus is that rehabilitation should be implemented as early as possible to take advantage of the neuronal compensation which proceeds symptoms (Bartlett et al., 2019; Busse et al., 2017; Cruickshank et al., 2018; Khalil et al., 2013; Paulsen et al., 2014; Quinn & Busse, 2017; Quinn et al., 2020; Reilmann et al., 2014; Ross & Tabrizi, 2011).

5.1.2 Multi-disciplinary Intervention in HD

Several prominent longitudinal studies of intensive multi-disciplinary team (MDT) rehabilitation in HD have reported beneficial outcomes (Bilney & Pearce, 2011; Fritz, 2017; Yomtoob et al., 2019). Despite the high prevalence of dysphagia and the significant consequences of this impairment, many of these rehabilitation interventions do not exclusively target swallowing impairment. Firstly, Zinzi and colleagues (2007; 2009) reported a landmark pilot study, retrospective case series and audit of 40 patients with early- to mid-HD who took part in three-week blocks of inpatient intervention repeated up to three times per year. Twenty-five participants completed all three admissions. Treatment included PT, occupational therapy (OT) and SLT intervention of four to eight hours per day, six days per week (Zinzi et al., 2007). Treatment was well tolerated with no reported adverse effects. Immediately following

treatment, highly significant improvements were reported in motor performance and ADLs using validated outcome measures ($p < 0.01$). There was no evidence of generalisation between admissions, however, no motor decline was observed over two years which may be significant in this degenerative disease (Zinzi et al., 2007). A non-standardised written questionnaire was posted to all participants who had taken part on average 8.6 months post-treatment. Of note, 91.1% (n = 34) of respondents were caregivers which may introduce a potential reporting bias. Significant improvements were reported in mood, apathy and social relationships ($p < 0.05$). Respondents also reported beneficial effects on gait, reduced falls and motor control. These improvements were reportedly maintained one to three months post-intervention in 71% of participants (Zinzi et al., 2009).

Piira and colleagues (2013, 2014) reported the effects of an intensive residential rehabilitation programme after one and two years (Piira et al., 2013; Piira et al., 2014). These studies replicated the intervention protocol previously described within Zinzi et al., (2007) above. MDT intervention included muscle strengthening exercises aimed to maintain function. Thirty-seven patients with early-mid HD took part in intervention; 31 completed all three admissions over one year. Measurements of ADLs and UHDRS ratings remained stable, and significant improvements in gait, balance, QoL, anxiety and depression were reported (Piira et al., 2013). van Walsem et al. (2018) reported a secondary analysis of the cognitive measures of this group following one-year of intervention. They reported significant decline in the Symbol Digit Modalities Test, but no other significant differences in the remaining seven neuropsychological measures, representing a stability of cognitive performance over longitudinal follow-up (van Walsem 2018). A two-year retrospective evaluation reported that six participants had ongoing improvements in QoL, anxiety and body mass index, but did not reach statistical significance. (Piira et al., 2014). Four out of six patients demonstrated non-significant improvements in

motor performance. Importantly, no decline in gait, balance, ADL performance or cognition was observed (Piira et al., 2014). Frich et al. (2014) investigated patient and caregiver perspectives of this intensive MDT rehabilitation programme with semi-structured interviews. Eleven patients out of 31 who completed the one-year intervention were invited to take part. It is not clear how the 11 participants were selected which may increase the risk of bias using motivated and well-supported patients and families. Results were similar to the Zinzi et al., (2009) with self-reported long-term improvements in balance, walking, social experiences and self-confidence post-treatment (Frich et al., 2014).

Ciancarelli and colleagues (2013, 2014 & 2015) described a combined PT and OT neuromotor rehabilitation protocol. PT intervention aimed to maintain control during specific exercises and improve postural stability and proprioception. OT aimed to restore functional ability to perform ADLs with improved dexterity and general motor control. SLT intervention was not included in this MDT study. Thirty-four individuals completed an intensive neurorehabilitation programme during a three-week hospital admission. Intervention was at least four hours per day, six days a week. There were significant improvements in all validated clinical, functional and physiological outcome measures post-intervention (Ciancarelli et al., 2015).

Another series of three studies described a randomised control trial (RCT) of patients with early to mid-stage HD (n = 22) who received either daily outpatient MDT intervention or usual care over nine months (Cruickshank et al., 2018; Cruickshank et al., 2015; Thompson et al., 2013). Training was individualised with one PT clinic session of group exercises and three self-directed home sessions of muscle strengthening and fine motor exercises per week. In addition, one session of OT every two weeks focused on cognitive and executive function skills (Cruickshank et al., 2015). Each session lasted 60 minutes. There was high adherence to clinic-

based group exercises (85%) and lower adherence to the home programme (56%). No adverse effects were reported but two people withdrew during treatment for unspecified reasons. Primary outcomes included the UHDRS, QoL questionnaires, a battery of neuropsychological tests and physical measures. Raters were blinded to intervention received. Significant improvements were reported in manual dexterity and lower limb muscle strength compared to the control group who significantly deteriorated. No significant differences in upper limb strength, balance or QoL scales were noted (Cruickshank et al., 2018). However, there was greater deterioration of stability in the control group and a moderate treatment effect was identified on UHDRS total motor scores and walking (Cruickshank et al., 2015). Cruickshank et al. (2015) also reported MRI outcomes of 15 participants who received the same methodological intervention protocol over nine months. It is unclear if this study evaluated the same group of patients described in the 2013 and 2018 studies. MRI studies pre- and post-intervention indicated significantly increased volume in the right caudate and bilaterally in the dorsolateral prefrontal cortex following nine months of multidisciplinary rehabilitation. Further, this study identified a significant association between the grey matter volume increases in the dorsolateral prefrontal cortex and improved performance on verbal learning and memory. This provided evidence that outpatient rehabilitation may increase neurogenesis or alter neuronal morphology through environmental enrichment, termed 'experience-dependent plasticity' (Cruickshank et al., 2015). Of note, these studies evaluated the effectiveness of a less intensive outpatient rehabilitation protocol (4 to 5 hours per week) compared to other intensive inpatient MDT interventions (4 to 8 hours per day) (Ciancarelli et al., 2015; Piira et al., 2013; Zinzi et al., 2007). This less intensive task-specific rehabilitation resulted in fewer significant improvements but was still sufficient to maintain function across physiological measures.

More recently, two exploratory studies have evaluated the effects of outpatient MDT intervention in individuals with premanifest HD. Firstly, Bartlett and colleagues (2019) completed MDT intervention which included physical exercises (aerobic and resistance), computerised cognitive training, dual-task training, sleep hygiene and nutritional guidance and socialisation over nine months. Sixteen individuals with premanifest HD completed three training sessions per week. Although there was no control group, this MDT program was designed to provide a systematic rehabilitative approach with a training program split into six blocks to avoid overtraining (Bartlett et al., 2019). Outcome measures were acquired from sleep studies and MRI studies pre- and post- intervention. Immediate and delayed memory consolidation was also assessed using objective outcomes. The authors reported large and medium effect sizes for sleep quality (rapid eye movement latency $d = 1.297$) and total time asleep ($d = 1.021$) following intervention. MRI analysis found significantly reduced volume of the right nucleus accumbens post-therapy ($p = 0.04$). There were no significant differences in subcortical structures or memory outcomes, which may reflect the need for more intensive intervention to elicit neural and functional change. The second study evaluated the same MDT program as that described by Bartlett and colleagues (2019) in 17 individuals with premanifest HD over nine months. This study by Reyes and colleagues (2020) evaluated the effects of this MDT intervention on dual-task abilities. Assessment sessions pre- and post-intervention consisted of simultaneous completion of arithmetic and torque steadiness tasks. Participant performance during single and dual-tasks were compared. Significant improvements in one progressive subtraction test ($p < 0.05$) were reported post-therapy and significant improvements in dual-task performance. As this was exploratory work, no control group was included in this study; however, this preliminary data suggests that MDT intervention is well tolerated and may have beneficial effects on dual-task performance through reduction of cognitive and motor interference in individuals with premanifest HD (Reyes et al., 2020).

Several home-based rehabilitation programs using technology such as computerised cognitive training, computer games or videos have reported positive adherence and clinical outcomes (Busse et al., 2013; Busse et al., 2016; Kempnich et al., 2017; Khalil et al., 2013; Kloos et al., 2013; Metzler-Baddeley et al., 2014; Sadeghi et al., 2017; Yhnell et al., 2020). Identified barriers to self-directed home rehabilitation included poor motivation, reduced caregiver support, frustration during the tasks and inability to implement the training into the daily routine (Yhnell et al., 2020). Low intensity rehabilitation (e.g. twice weekly) described in some of these home programs was identified as insufficient to obtain systematic improvements as measured by standardised outcomes Quinn et al. (2014), therefore daily rehabilitation was typically recommended.

5.2 Treatment Approaches for Corticobulbar Symptoms

Promising evidence exists to support implementation of intensive rehabilitation to target corticospinal and cognitive symptoms of HD. However, there is a paucity of evidence for treatment of corticobulbar symptoms in HD. A recent review of treatment options in HD concluded, "we recommend speech and swallow therapy before the onset of significant dysphagia" (Wyant et al., 2017, p. 33); however, referral rates for SLT are amongst the lowest of all ancillary services at 3.01% in HD (Yomtoob et al., 2019).

5.2.1 Compensatory Management

As evidence to support rehabilitation of corticobulbar symptoms in HD is lacking, SLT intervention typically includes ongoing assessment and monitoring (Hunt & Walker, 1989; Mariscal et al., 2014; Pizzorni et al., 2020). Historically, neurodegenerative dysphagia intervention comprised of compensatory strategies and advice to promote safe swallowing; this continues to be the primary management in HD (Clarke et al., 2018; Hamilton et al., 2012;

Hunt & Walker, 1989; Keage et al., 2020; Zimmerman et al., 2020). Treatment is aimed to minimize the impact of dysphagic symptoms, reduce the risk or impact of secondary complications, and educate individuals to facilitate more enjoyable mealtime experiences (Heemskerk & Roos, 2011; Stewart, 2012). However, these compensatory strategies can have significant negative effects on QoL and participation, as discussed further below (Clarke et al., 2018).

5.2.1.1 Diet Modification

Diet and fluid modification aimed to alter bolus transport and optimise swallowing safety is the most common SLT intervention for dysphagia in HD (de Tommaso et al., 2015; Hamilton et al., 2012; Leopold & Kagel, 1985; Pizzorni et al., 2020). Although appropriate use of diet and fluid modification is assumed to reduce the risk of choking or aspiration, (Hamilton et al., 2012) the effectiveness to improve swallowing safety and subsequent reduction in aspiration pneumonia has not been documented in HD. These recommendations are often made without instrumental assessment (de Tommaso et al., 2015), and may be inappropriately restrictive. Reduced palatability of thickened liquids and poor adherence to recommendations has correlated to increased risk of dehydration, malnutrition, urinary tract infections and decreased QoL (Beck et al., 2018; Espinosa-Val et al., 2020; Newman et al., 2016).

5.2.1.2 Non-oral Feeding

Non-oral or artificial enteral feeding approaches such as percutaneous endoscopic gastrostomy (PEG) may be recommended in late stage HD if oral intake is insufficient or there is a substantial risk of aspiration (Hamilton et al., 2012; Sarkar et al., 2017; Schradt et al., 2018; Sussmuth et al., 2012). Two preliminary studies have recently conducted retrospective chart reviews comparing clinical outcomes of patients with HD who did and did not have PEG

feeding. The first is a conference abstract which reviewed 148 patients with HD. This study reported that the group with PEG tubes lived longer (p = 0.02), however there were significantly higher prevalence of skin ulcers ($p < 0.001$) and rates of aspiration pneumonia from 35% to 77% in those with PEG ($p < 0.001$) (Dyke & Frank, 2019). Similar results were reported by Hamedani et al. (2020), this large cross-sectional study compared outcomes in HD inpatients (n = 1614) and MND inpatients (n = 7908) with gastrostomy placement. There were significantly poorer outcomes for the HD group, ($p < 0.0001$) with higher prevalence of sepsis, extended hospital stay and aspiration pneumonia rates increased from 20.5% in the MND group to 34.1% in the HD group (Hamedani et al., 2020). Despite this lack of evidence, non-oral feeding is recommended on a case by case basis in HD as well as other neurodegenerative diseases such as PD and MND (Stavroulakis & McDermott, 2016). Decisions about non-oral feeding should be carefully considered based on the individual's beliefs and wishes as part of advanced care planning (Stavroulakis & McDermott, 2016).

5.2.1.3 Postural Changes and Compensatory Manoeuvres

The use of adapted utensils and customised chairs for postural modification have been reported in several studies (Hunt & Walker, 1989; Kagel & Leopold, 1992). Strategies included presentation of food below waist level, weighted cups, wrist weights and trunk stabilisation with ankle weights to reduce tachyphagia and premature oral transfer (Kagel & Leopold, 1992). Postural changes with adaptive seating reportedly improved clearance of residual after swallowing, but no instrumental measures were reported to verify this (Hunt & Walker, 1989). Another study evaluated the effect of a specialist chair which promoted "adapted position of the head" (Woisard et al., 2020, p. 180). This study included 56 patients with identified dysphagia (n = 12 with HD). Swallowing safety and hyoid movement was evaluated with VFSS. The examiners were blinded for this RCT, patients who utilised the chair for four weeks

(n = 26) had a measurable increase in hyoid excursion but no other differences were identified with PAS or self-reported QoL (Woisard et al., 2020).

Altered head postures such as adoption of a chin tuck position prior to oral transfer are reported to be effective strategies in HD (Giddens et al., 2010). This is based on assumptions that a chin down posture could improve BoT to posterior pharyngeal wall approximation and increase the vallecula space to improve swallowing safety (Welch et al., 1993). Neither of these assumptions have been confirmed in other populations. Two preliminary studies have evaluated chin tuck posture during swallowing in HD. Heemskerk et al. (2015) subjectively rated swallowing features during chin down posture compared to neutral head posture during 10 ml bolus swallows on VFSS. Fourteen out of 45 patients (31%) were unable to adopt an adequate chin tuck position. The authors reported no significant differences observed in pre-swallow spillage, aspiration or post-swallow residue between the two postures. The second study described chin tuck and diet modification as 'effective' to prevent aspiration in HD as measured with FEES (Schradt et al., 2018). This grey literature conference abstract described by Pizzorni and colleagues (2020) does not include sufficient detail to allow for replication or critical appraisal of these findings. These compensatory strategies should be trialled with instrumental guidance (Daniels et al., 2019), and may be contraindicated in cases where oral control, spillage and dysmotility may be exacerbated.

The clinical guidelines for management of dysphagia in HD recommends the implementation of cued cough post-swallow and additional clearing swallows during mealtimes to reduce risk of aspiration (Hamilton et al., 2012). No specific studies have evaluated the effectiveness of these techniques in HD. In other neurogenic aetiologies voluntary airway closure such as supraglottic or super-supraglottic swallowing manoeuvres may be implemented to improve

airway protection (Logemann, 1998). Whilst preliminary evidence suggests the supraglottic swallowing manoeuvre may have a beneficial effect on swallowing biomechanics in healthy older individuals (Seong et al., 2018), further evidence is required to evaluate the effectiveness of this technique in neurogenic dysphagia.

5.2.1.4 Sensory Stimulation

Strategies to enhance sensory input to the CPG may be implemented as another compensatory intervention to improve swallowing efficiency in patients with neurogenic dysphagia (Pelletier & Lawless, 2003). Kagel and Leopold (1992) reported the use of thermal or gustatory enhanced stimuli (iced lemon chips) before and after oral trials during VFSS as part of a number of compensatory strategies with HD patients. The authors reported improved swallowing safety and efficiency, but the specific effect of this additional sensory stimulation has not been explored in HD. In other neurogenic groups, significant improvements in swallowing outcomes have been reported using cold (Cui et al., 2020; Michou et al., 2012), sour (Cola et al., 2012; Logemann et al., 1995; Pelletier & Lawless, 2003) or carbonated boluses (Bülow et al., 2003; Sdravou et al., 2012). In contrast, the use of thermal-tactile stimulation (Logemann, 1983; Regan et al., 2010; Rosenbek et al., 1996b) and neuromuscular electrical stimulation techniques have also been reported to enhance sensory input to the CPG and improve the swallowing response (Mistry et al., 2012; Rofes et al., 2014b). The effectiveness and specificity of these techniques in treatment of dysphagia is developing and several inconsistent or conflicting results have been reported in the literature (Baijens et al., 2013b; Bath et al., 2016; Jayasekeran et al., 2010; Rofes et al., 2014b). In addition, evaluation of these techniques has not yet extended to neurodegenerative conditions such as HD.

5.2.2 Dysphagia Rehabilitation[1]

There is a lack of evidence evaluating the efficacy of rehabilitation targeting corticobulbar symptoms in HD, therefore this section will include evidence in other neurological aetiologies. The lack of rehabilitative approaches for dysarthria and dysphagia treatment in HD may be due to a historical clinical fear of detrimental treatment effects including "the possibility of inducing further weakness with strengthening attempts" (Giddens, 2010, p. 3). Importantly, there is insufficient evidence to suggest that intensive rehabilitation of corticobulbar symptoms in other neurodegenerative populations is contraindicated (Athukorala et al., 2014; El Sharkawi et al., 2002; Plowman, 2015; Troche et al., 2011).

5.2.2.1 Strength-based Approaches in HD

Very few studies have systematically evaluated traditional strength-based dysphagia training in HD. Those that have are limited to expiratory muscle strength training (EMST), oromotor exercises and Mendelsohn-Masako combined manoeuvres. Firstly, in the pioneering HD intervention study, Leopold and Kagel (1985) provided an overview of their dysphagia intervention, however the duration and content of therapy sessions was not specified to allow for replication. Intervention included a modified Valsalva manoeuvre (forced exhalation against a pinched nose) and compensatory strategies (diet modification, adaptive utensils, optimum positioning). An unspecified number of the patients with severe dysphagia required non-oral feeding to maintain nutrition and hydration via nasogastric tube until the "compensatory techniques could be instituted and a pureed diet could be safely tolerated" (Leopold & Kagel, 1985, p.59). Patients were also taught the 'chew-swallow-cough-swallow' technique. The authors reported that eight out of 12 patients returned to a normal diet. The

[1] Portions of this section of the literature review have been published as part of: Burnip, E., Wallace, E., Gozdzikowska, K., & Huckabee, M. L. (2019). A systematic review of rehabilitation for corticobulbar symptoms in adults with Huntington's Disease. *Journal of Huntington's Disease, 9*, 1-12.

"more severely demented patients required more sessions" (Leopold & Kagel, 1985, p.60) and greater ongoing supervision post-therapy to target more severe cognitive and motor sequencing deficits; however, this additional therapy was not defined. This study design was vulnerable to several identified biases. Blinding of raters was not possible, outcome measures were not validated, or consistently repeated post-therapy. In addition, data analysis of quantitative outcome measures was not conducted.

Giddens et al. (2010) evaluated a home program of SLT intervention over two years with a descriptive case series (n = 13 early stage and n = 1 late stage HD). The authors reported swallowing screening and referrals for baseline VFSS where appropriate, but no further information was provided regarding how many participants underwent VFSS or the findings. Treatment consisted of oral motor labial and lingual resistance training, respiratory (glottal adduction) and phonatory exercises completed twice daily at home, a minimum of four times per week. The participant with late stage disease withdrew due to perceived weakness, however this was not measured. Improvements in oromotor outcomes such as increased phonation time, improved labial range of movement and reduced vowel distortion were reported in all other participants, but the length of treatment and time of follow-up were not specified. A further pilot study, reported within the same manuscript, evaluated the same home program over 30 days in five individuals with mild dysarthria secondary to HD. Outcome measures included cranial nerve examination, speech diadochokinetic rates and maximum phonation time measured by unblinded raters. The number of participants that fully adhered to the exercise program was not reported in either study. Again, descriptive improvements in oromotor tasks and perceived improvements in resonance and vocal control were described for all participants. 'Elimination' of dysphagia was reported in two case studies, although no swallowing outcome measures were included. In addition, two participants began anti-choreic drug treatment mid-

study. These studies had a high risk of selection and reporting bias, however, the perceived functional oromotor improvements justifies further research using objective swallowing outcomes to measure any effect of rehabilitation.

EMST is another strengthening intervention which involves exhaling into a device with a one-way valve set at a resistance threshold of between 60% and 80% of the individual's maximum expiratory pressure. Although EMST aims to strengthen expiratory cough, the training requires recruitment of the oropharyngeal and laryngeal musculature integral to swallowing which can indirectly improve swallowing biomechanics (Kim & Sapienza, 2005). In healthy adults, EMST has been shown to specifically increase activation of the submental muscles as measured with sEMG (Burkhead et al., 2007). Reyes et al. (2015) evaluated EMST and inspiratory muscle training in 18 patients with mid-stage HD. Nine patients were randomised to complete expiratory and inspiratory muscle training and nine received a fixed resistance placebo exercise. Exercises were completed six times per week for four months. Spirometry indices, maximum inspiratory and expiratory pressure, TWST, gait, dyspnoea and swallowing QoL measures were completed pre- and post-intervention. Respiratory outcome measures and swallowing QoL improved in the intervention group. Treatment had a small positive effect on swallowing time as measured by the TWST, however no other measures of swallowing biomechanics were included (Reyes et al., 2015). In addition, a small positive effect was demonstrated in the control group, which was also reported in Jones et al. (2016). Jones et al. (2016) completed another pilot study of 20 participants with early HD who were randomly allocated to training or placebo groups. Intervention consisted of inspiratory muscle training with 50% resistance, twice per day for six weeks. Swallowing was not evaluated in this study. Adherence to the therapy protocol was reported as good (70% ± 26.35%). There were no significant differences in inspiratory muscle strength, peak cough flow or sit to stand results in

response to training. Interestingly, both the training and placebo breathing exercises increased peak cough flow and inspiratory sniff nasal pressure post-intervention, which could indicate increased respiratory efficiency with breathing tasks without the need for strengthening or resistance training (Jones et al., 2016).

In addition to these two studies in HD, preliminary research evaluating EMST in other neurodegenerative populations such as PD and MND has shown treatment effects on swallowing safety and efficiency (Plowman et al., 2019; Troche et al., 2010; Van Hooren et al., 2014). An initial pilot study by Plowman and colleagues (2016) evaluated EMST in patients with MND (n = 15). Training consisted of 50% maximum expiratory pressure representing a moderate training load, five days per week for eight weeks. Seventy-nine percent of patients completed the protocol. Of the six objective measures of swallowing biomechanics from VFSS, a significant treatment effect of increased maximum hyoid displacement was reported, but no other differences in swallowing outcomes were observed (Plowman, 2016). A further double blinded RCT evaluated the same protocol in a larger MND cohort (n = 48). There were no significant improvements in swallowing function observed on VFSS. There was, however, significant deterioration in the sham group post-therapy. As this deterioration was not observed in the intervention group, this result could be clinically significant.

Additionally, Troche and colleagues (2010) completed a blinded RCT of EMST in patients with PD (n = 60). In contrast to the previous studies, this treatment was five days per week over four weeks set at 75% of the participant's maximum expiratory pressure. Despite the reduction in intervention duration, a moderate positive treatment effect (d = 0.55) was reported for PAS ratings. There were no significant differences in VFSS hyolaryngeal timing and

displacement measures post-treatment. Of note, the hyolaryngeal measures were obtained during 10 separate 5 ml liquid bolus trials, whilst the PAS ratings were judged during 3 oz sequential swallowing. It was not clearly defined how the sequential swallowing task was rated using PAS, for instance if the best, worst or all swallows were included in analysis. In addition, the average PAS scores were subject to statistical analysis. This method of analysis with this categorical outcome has been criticised and may have affect the validity of results (Steele & Grace-Martin, 2017). The intervention group had a mean PAS of 2 pre- and post- therapy which falls within the normal limits of swallowing (Garand et al., 2019; Humbert et al., 2018; Steele et al., 2019). The discrepancy in treatment effects may indicate a ceiling effect where swallowing biomechanics may not significantly change in a group with relatively mild dysphagia. Self-reported QoL as measured by the SWAL-QoL significantly improved ($p < 0.05$) for both the intervention and sham groups. As observed in the previous study (Plowman et al., 2016), this study in PD also reported significant deterioration in the sham group which was not observed in the intervention group (Troche et al., 2010). This study, however, did not include any follow-up assessments to evaluate any maintenance effects. These studies suggest promising beneficial effects of intensive strength training in neurodegenerative populations; which has historically been presumed to be detrimental.

The Mendelsohn manoeuvre is a voluntary prolonged hold of laryngeal elevation at the height of swallowing. This technique has traditionally been described to increase laryngeal elevation, maximum hyoid excursion and prolong UES opening to improve efficiency of bolus transport into the oesophagus (McCullough & Kim, 2013). Transient changes in biomechanics have been reported in healthy participants during this manoeuvre (Hoffman et al., 2012; Inamoto et al., 2018). Additionally, the Masako or tongue-hold manoeuvre is a task-specific strengthening exercise which requires the patient to hold their tongue anteriorly between the teeth during dry swallows. This task aims to increase activation and anterior movement of the posterior

pharyngeal wall resulting in improved approximation with BoT during swallowing (Fujiu & Logemann, 1996; Logemann, 1998). Preliminary evidence in dysphagic patients (n = 3 following head and neck cancer) suggests that this exercise can increase pharyngeal pressures during swallowing (Lazarus et al., 2002); however, this increase was not replicated in healthy participants (Doeltgen et al., 2009; Hammer et al., 2014).

One study in HD included the use of the Mendelsohn manoeuvre with the Masako (Heemskerk, 2016). Thirty patients received dysphagia intervention which included the Masako and Mendelsohn manoeuvres, although further details of dosage were not specified. One patient received a video from her VFSS as biofeedback to aid task performance. Heemskerk (2016) reported that 'most' patients could complete the tasks and reported treatment benefits, although no objective outcome measures were reported. The authors concluded that from patient self-report, these swallowing manoeuvres may be beneficial for people with HD. This grey literature requires more description of methods, training protocol and swallowing outcome measures before any assumptions of effectiveness can be made. The use of these manoeuvres with elderly or neurodegenerative populations has been limited due to concerns about fatigue of musculature and difficulties completing the task at every meal particularly when cognition is affected (McCullough & Martino, 2013).

5.2.2.2 Other Strength-based Training Approaches

Although there are no data relative to HD, there are other strength training approaches reported in the swallowing literature. These include lingual strengthening exercises against resistance using the Iowa Oral Performance Instrument (IOPI), the Shaker or 'head-lift' exercise, chin tuck against resistance and effortful swallowing. Each of these approaches have preliminary evidence to suggest changes in oropharyngeal musculature resulting in measurable

improvements in swallowing safety and efficiency (Hind et al., 2001; Hiss & Huckabee, 2005; Huckabee & Steele, 2006; Kim & Park, 2019; Robbins et al., 2007; Shaker et al., 2002; Watts, 2013; Wheeler-Hegland et al., 2008).

Strength-based approaches dominate the swallowing rehabilitation literature at present which likely reflects the lack of diagnostic specificity of current assessment techniques for swallowing (Huckabee & Macrae, 2014). For instance, visualisation of reduced movement of anatomical structures and post-swallow residual on FEES or VFSS may lead the clinician to assume weakness when the underlying biomechanical dysfunction is unknown. As the underlying motor deficit in HD is not primary weakness, strength-based rehabilitation is unlikely to improve swallowing dysfunction and could, at worst, exacerbate the impairment. A transition towards skill-based swallowing rehabilitation is developing in the literature (Zimmerman et al., 2020), this alternative approach may be beneficial in HD to maximise neuroplasticity and facilitate functional behavioural change as described in the corticospinal literature (Quinn & Busse, 2017; Quinn et al., 2013a). Zimmerman et al. (2020) proposes that skill-based rehabilitation approaches should be embedded within strength-based approaches to facilitate neural modulation and elicit long term swallowing recovery.

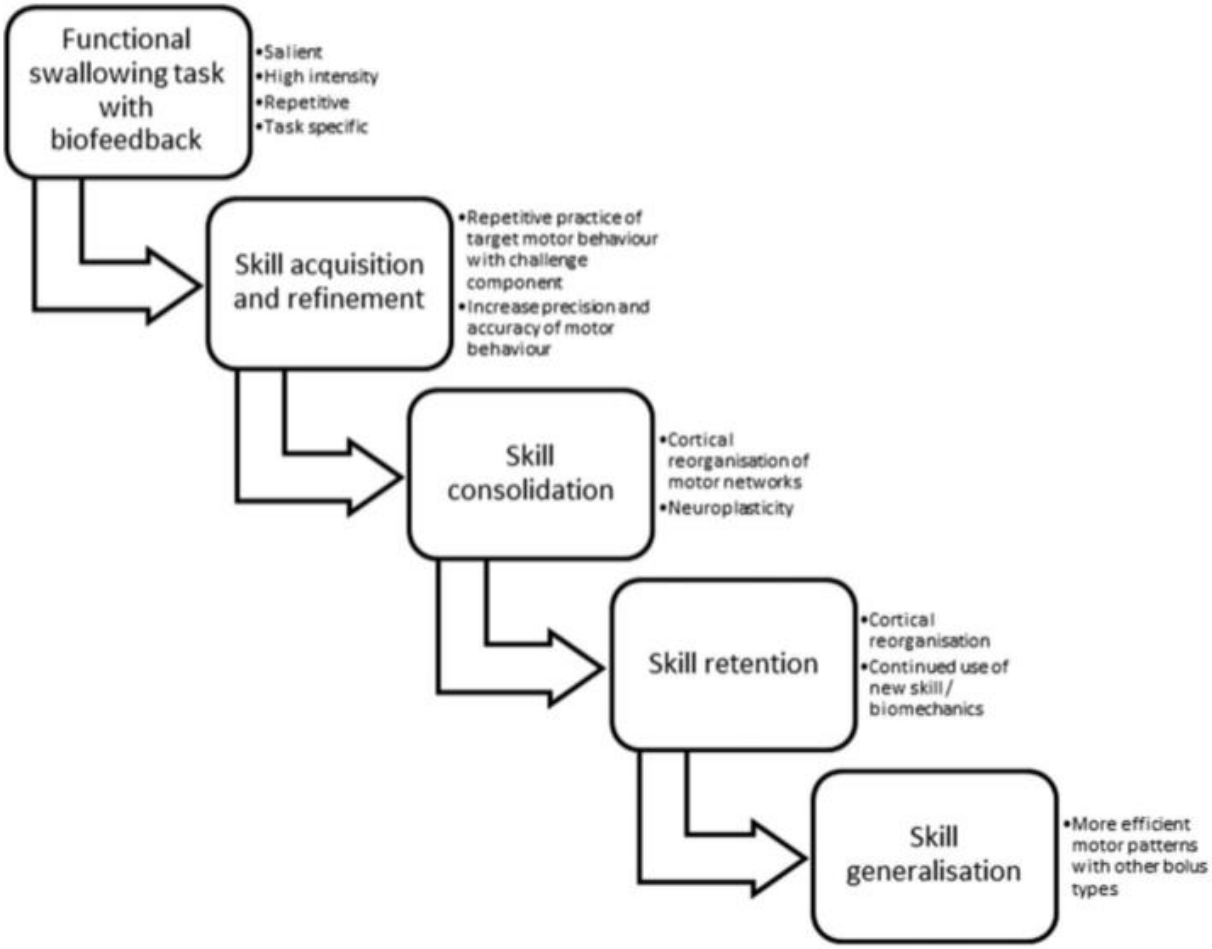
5.2.2.3 Skill-based Dysphagia Training

In the context of swallowing, skill training includes the ability to "voluntarily modulate the timing, and coordination of multiple muscles and anatomical structures involved in deglutition to acquire skill in specific aspects of swallowing biomechanics at a central level" (Huckabee & Burnip, 2018, p.147). There is increasing evidence to support the potential for voluntary modification of both oral and pharyngeal parameters of swallowing biomechanics (Lamvik et al., 2015; Wheeler-Hegland et al., 2008). Exercises to consciously modify swallowing are

associated with increased activation of several neural regions which may promote neural plasticity (Malandraki et al., 2011; Peck et al., 2010; Svensson et al., 2003). Figure 5.2 represents the process of skill-based dysphagia training and how, unlike other approaches, the principles of skill acquisition and motor learning are embedded within this framework.

Figure 5.2

Proposed Model of Skill-based Swallowing Training



Note. This framework incorporates the principles of motor learning and skill acquisition to facilitate neuroplasticity and cortical modulation of swallowing biomechanics. Reprinted with permission from: "Still Rethinking Rehab: Motor Learning Treatment Approaches for Dysphagia," by Huckabee, M. L., & Burnip, E., 2018, *Perspectives of the ASHA Special Interest Groups*, 3(13), 146-156, doi:10.1044/2018

Skill-based training protocols include salient, high-intensity, swallowing tasks. Biofeedback is utilised to increase the precision and accuracy of the motor behaviour (Krakauer, 2006; Zimmerman et al., 2020). The use of biofeedback in skill training has been suggested to

facilitate intrinsic learning of more complex motor sequences and aid skill retention in healthy individuals (Wilkinson et al., 2015) and in HD (Gordon et al., 2000; Willingham et al., 1996). Exercises which facilitated sensorimotor integration using biofeedback allowed patients with HD to modify the coordination and timing of the motor task to improve the overall motor sequence (Gordon et al., 2000; Quinn et al., 2001). One commonly utilised method to provide biofeedback is sEMG. The use of sEMG biofeedback within challenging swallowing tasks can aid volitional control improve the motor skill (Azola et al., 2017). Several studies have described the training of strength-based effortful swallowing tasks using sEMG as a biofeedback modality (Crary et al., 2004; Huckabee & Cannito, 1999). sEMG of the submental muscles during swallowing rehabilitation is acceptable, non-invasive, salient representation of a complex internal mechanism (Archer et al., 2020; Macrae et al., 2014).

5.2.2.4 Swallowing Intervention Incorporating Skill-based Principles

The implementation of skill-based dysphagia intervention has developed over the last few years. The earliest incorporation of skill-based approach combined with strength training was The McNeil Dysphagia Therapy Program (MDTP) (Crary et al., 2012). This systematic exercise protocol, based on the principles of motor learning, consists of a hierarchical presentation of tasks which includes increasingly challenging bolus volume, consistency and eating rate. Lan et al. (2012) described normalisation of swallowing biomechanics in eight patients with chronic dysphagia who completed 15 sessions of MDTP, 1 hr per day over three weeks of therapy. Dysphagia was secondary to oropharyngeal cancer treatment (n = 5), unspecified neurological disease (n = 1) or these causes combined (n = 2). Although MDTP is task-specific, the focus is on progressive strengthening and coordination using “effortful type” swallowing and is not aimed at specific biomechanical deficits. This study compared patients’ temporal coordination of swallowing as measured by lingual-palatal and pharyngeal

manometry to a healthy control group. Post-therapy, there were significant improvements in pharyngeal manometric parameters with the greatest treatment effect observed with thin fluids. These investigators suggested that increased speed of pharyngeal swallowing initiation reflected improved efficiency, coordination and neuromotor reorganisation of swallowing control (Lan et al., 2012). All participants increase functional oral intake post-therapy ($p < 0.05$) as 4 out of 7 patients returned to full oral intake. Although improved swallowing safety is inferred, there were no instrumental outcomes to evaluate this and no follow-up period to measure skill-retention.

Crary, et al. (2012) also evaluated the MDTP in nine patients with chronic dysphagia (n = 6 from oropharyngeal cancer treatment, n = 2 from unspecified neurological disease and n = 1 combined causes). It is unclear if this sample included the same patients as the last study. The same protocol was implemented as described above. Functional and instrumental measures of swallowing biomechanics were utilised pre- and post-therapy and analysed by a blinded assessor. In addition to Lan and colleagues (2012), this study incorporated VFSS outcome measures, sEMG of the submental muscles and included a three-month follow-up assessment. All patients significantly improved in functional outcomes immediately post-therapy with no reported de-training effects at three-month follow-up. Positive changes in swallowing biomechanics measured by VFSS were also reported, but these were not significant across all bolus consistencies. Again, 4 out of 7 patients returned to oral intake and at three months their feeding tubes were removed. This study provides preliminary evidence that MDTP elicits measurable change in swallowing biomechanics with evidence that these treatment effects were maintained after three months. A later study evaluating the effects of MDTP on swallowing biomechanics also reported positive clinical outcomes (Sia et al., 2015). Eight patients with the same aetiology as described in Lan et al., (2012) demonstrated positive changes in swallowing

biomechanics as measured via VFSS, specifically, hyoid and laryngeal excursion, duration and velocity increased. Five out of six patients returned to full oral intake post-therapy. Again, the authors hypothesised that these changes in swallowing biomechanics following rehabilitation resulted in more efficient and safer swallowing (Sia et al., 2015). This study focussed on objective measurements of hyolaryngeal excursion. Other elements of swallowing biomechanics, such as pharyngeal constriction ratio or UES opening could have been measured on VFSS to fully evaluate the treatment effect on safety and efficacy of swallowing. These MDTP studies are limited by small sample sizes in patients with mixed aetiologies. It would be beneficial to further evaluate the effectiveness of MDTP in specific neurogenic conditions with larger control trials.

Two recent single case studies have presented preliminary positive effects with a patient with PD and a patient following anoxic brain injury (Curtis et al., 2020a; Curtis et al., 2020b). Of note, both of these patients had cognitive impairment and previous intensive strength training (Masako manoeuvre and EMST) had resulted in negligible improvements. Treatment consisted of four sessions of respiratory-swallowing coordination training over four weeks. These sessions aimed to increase the frequency of an optimal "exhale-swallow-exhale" coordination pattern. Patients completed 70 swallows per session, optimal and suboptimal respiratory-swallowing coordination patterns were elicited during the first half of the session, then the second half included swallowing trials at optimal and suboptimal lung volume range. The PD patient also completed four sessions of additional voluntary cough skill training. This consisted of 80 voluntary cough trials, the patient was cued to vary their cough strength utilising a peak flow meter for biofeedback (Curtis et al., 2020a). These studies described mixed skill and strength training approaches aimed to improve respiratory-swallowing coordination and cough strength. For the patient with severe dysphagia secondary to PD, large effect sizes were

reported immediately following training with improvements in optimal respiratory–swallowing coordination and generalised improvements in swallowing safety with reduced post-swallow pharyngeal residual and PAS ratings as observed via FEES. This improvement in dysphagia severity was maintained two months post-therapy (Curtis et al., 2020a). The second case study reported improved frequency of optimal respiratory-swallowing patterns from 45% pre-therapy to 90% post-therapy which was maintained at three months follow up (Curtis et al., 2020b). Again, improvements in swallowing safety, efficiency, overall dysphagia severity were observed immediately post-therapy and were maintained at one-month follow-up. There were no direct timing or displacement measures of swallowing biomechanics included. Both studies used multiple baseline single-subject study designs, however, comparison is limited as different training protocols and follow-up periods were implemented. Both studies integrated several aspects of motor learning within the training, however, four sessions of respiratory-swallowing training over four weeks with no prescribed home practice between sessions represents a far lower intensity compared to other skill-based training protocols described in this section.

Martin-Harris et al. (2015) described a skill-based respiratory-swallowing training protocol. This novel protocol used respiratory-swallowing patterns as a biofeedback modality to train task-specific optimal coordination of respiration and swallowing. Thirty participants with chronic dysphagia following head and neck cancer completed one-hour training sessions, twice per week for a period of four weeks. A hierarchy of identification, acquisition and mastery motor skill acquisition tasks were stipulated with a minimum of 80% accuracy of the target response to progress to the next stage. Post-therapy, all patients implemented optimal respiratory-swallowing coordination patterns ($p < 0.001$). These optimal patterns were mastered by all patients within eight sessions. These changes correlated with significant

improvements in swallowing biomechanics as measured on VFSS and were maintained at one-month follow-up. The effectiveness of this respiratory-swallowing coordination training has yet to be evaluated in neurogenic dysphagia.

Another study has evaluated a combined strength and skill-based approach to lingual training (Steele et al., 2013). Six patients with oropharyngeal dysphagia secondary to acquired brain injuries completed at least two sessions of lingual training per week for 11 - 12 weeks. Each session included six blocks of 10 tongue pressure tasks using the IOPI (as previously described). The first two blocks elicited maximum anterior and posterior isometric tongue pressures. The subsequent four blocks required submaximal pressures in order to 'hit' a randomly selected target. Finally, a generalisation task including six cued saliva swallows with the IOPI held anteriorly was included. The sub-maximal task set targets at 20 - 90% of the patient's maximum isometric pressure capacity. Functional improvements were reported in reduced aspiration on thin fluids in five of the six patients. However, compared to pre-treatment, there was a deterioration in bolus clearance in the valleculae and pyriform sinuses as measured on VFSS. The extent to which lingual resistance training directly impacted on aspiration remains unclear, the authors hypothesised that this apparent improvement in swallowing safety may be attributed some spontaneous recovery of chronic dysphagia in response to targeted intervention. No follow-up assessments were conducted to measure any de-training effects. Although this programme contained a 'skill component', the task was not specific to swallowing with subsequent mixed outcomes observed in terms of swallowing efficiency and safety.

Although functional outcomes from these studies were generally positive; it is difficult to attribute these changes in swallowing to one element of the mixed skill and strength training

protocols. Preliminary studies have emerged focussed only on skilled submaximal swallowing performance without associated strengthening targets. Four proof of concept studies have evaluated a skill-based swallowing training in isolation using sEMG as a biofeedback modality. Athukorala and colleagues (2014) utilised a custom-made task-specific software (Biofeedback in Strength and Skill Training: BiSSkiT) to project the activity of the submental muscles via sEMG to a visual display. (Athukorala et al., 2014). Ten patients with dysphagia secondary to PD underwent two weeks of daily treatment. The treatment protocol consisted of 100 swallowing trials across 10 blocks, each separated with a 90 s break. This training required individuals to volitionally control the timing and amplitude of their swallowing in order to 'hit' a target box with the sEMG waveform. Notably, the treatment did not require maximal effort, as the target area utilised 20 - 70% of the participant's calibrated swallowing amplitude. This high intensity training also introduced a task specific challenge by adapting the size of the target in response to participants' successive performance. Functional parameters of swallowing as measured by the TWST, temporal sEMG measures and patient-reported swallowing related QoL all improved following treatment. Three patients changed medication regimes during this time which may have contributed to the observed changes. There were no improvements in measures from the TOMASS. The observed improvements were maintained two weeks after the cessation of treatment. This study did not include instrumental assessment to validate the positive findings; therefore, further research including VFSS would allow for visualisation of the safety and efficiency of swallowing biomechanics with different bolus types. In addition, a longer follow up period would be beneficial to evaluate skill retention in this neurodegenerative disease.

A second exploratory study utilised the same BiSSKiT software with sEMG biofeedback as part of swallowing rehabilitation in a patient with multiple systems atrophy (Perry et al., 2018).

Therapy consisted of one clinical session using the BiSSkiT software per week for six weeks, with additional daily home practice utilising a video guided audio-visual swallowing target (total 60 cued swallows at home per week). Despite the reduced intensity of this training protocol, there were substantial improvements in self-reported swallowing related QoL and swallowing biomechanics rated using FEES post-therapy. The unblinded authors reported pre-swallow spillage and aspiration were eliminated and post-swallow residual improved post-therapy. This case study, whilst promising, cannot be generalised until it is replicated with a larger patient cohort including a follow-up period. In addition, instrumental outcomes were subjectively judged as present or absent, therefore quantitative measurements of swallowing biomechanics would be more sensitive to represent any treatment effects.

A third feasibility study is a conference presentation which evaluated another skill-based training software with sEMG biofeedback (SilverFit Rephagia Training) in an outpatient clinic with seven mixed stage HD patients. Training consisted of three sessions of 45 min treatment. The number of swallowing trials per session was not reported. Six patients had sufficient attention and motivation during all sessions. This study included no swallowing outcome measures; patient feedback was described as 'positive' when asked by the clinician which could introduce a reporting bias. This study reported preliminary evidence that sEMG biofeedback is feasible with these patients (Kerkdijk et al., 2018), although further research including a larger sample size and objective outcome measures is required.

Finally, Stepp et al. (2011) evaluated a novel skill-based training using sEMG as biofeedback. This study placed sEMG electrodes bilaterally on the anterior neck muscles intended to measure activation of the thyrohyoid, sternohyoid and omohyoid muscles. Participants were not specifically required to complete swallowing events to modulate the muscle activity during

biofeedback, therefore task specificity was not optimised. Six healthy participants completed one training session consisting of 70 trials separated into 10 blocks with specified breaks between blocks. One patient with severe oropharyngeal dysphagia following brainstem stroke completed a total of six sessions over three weeks. The task required participants to volitionally control the amplitude of the waveform to control the actions of the video game characters moving across the screen. Healthy participants demonstrated higher target accuracy after one session compared to the dysphagic patient. After five further sessions, the patient's accuracy significantly improved. The authors also reported qualitative improvements in the patient's secretion management and perceived speed of volitional swallowing post-treatment. This study did not include any objective measures of swallowing biomechanics. However, these preliminary studies demonstrate potential benefits of sEMG biofeedback to facilitate motor learning in dysphagia rehabilitation. Of note, only one of these studies was in HD and two others in neurodegenerative diseases.

Other modalities of biofeedback have also been reported as part of a skill-based dysphagia training. Huckabee et al. (2014) utilised pharyngeal manometry as a biofeedback modality, allowing patients to visualise and modulate their pharyngeal pressure sequence during swallowing. Sixteen patients with varied aetiologies were identified using VFSS and pharyngeal manometry. Patients underwent intensive one-hour sessions, twice daily for a minimum of one week. Therapy utilised manometric biofeedback to increase the temporal distance between the peak pharyngeal waveforms during swallowing, thus approximating sequencing of pressure observed in healthy controls. Average latency between peak pressures increased from 15 ms to 137 ms after one week of treatment. This improvement correlated with a decrease in average swallowing duration and a functional improvement in oral intake with 11 out of 16 patients eventually returning to normal diet. Again, changes in swallowing

biomechanics were not validated with post-therapy VFSS to visualise swallowing safety and efficiency. The number of treatment sessions was not specified, however four of the five patients who were unable to continue intensive treatment for more than one week did not return to full oral intake. Further evaluations with a consistent treatment protocol and follow up period would be beneficial to aid generalisation of this promising skill-training.

5.2.3 Summary

Historically, SLT management of HD has focused on compensatory approaches such as diet modification, increased supervision and postural changes (Kagel & Leopold, 1992; Leopold & Kagel, 1985). Although a lack of high-quality evidence exists to justify the effectiveness of swallowing rehabilitation in HD, there is evidence from corticospinal literature that rehabilitation has significant functional benefits which may be replicated for treatment of dysphagia.

In HD, corticobulbar deficits are not characterised by muscle weakness (Kagel & Leopold, 1992; Manor et al., 2018); therefore, skill-based training, focusing on precision of neuromuscular connections is an appropriate rehabilitation approach. Preliminary studies in other neurodegenerative diseases have reported promising results following skill-based dysphagia rehabilitation (Athukorala et al., 2014; Curtis et al., 2020a; Kerkdijk et al., 2018; Perry et al., 2018; Troche et al., 2011). Utilisation of a skill-based approach could maximise the early neuroplasticity documented in HD to promote neural modulation through progressive and challenging error-based learning (Bastian, 2008; Jensen et al., 2005; Zimmerman et al., 2020). As hypothesised in Figure 5.1 (p.88), intervention to optimise the early stage neural re-organisation in HD could maintain function and improve QoL (Andrews et al, 2015). Current skill-based literature in neurodegenerative dysphagia is limited by a lack of quantitative

measures of swallowing safety and efficiency. To address these gaps in our knowledge, detailed and replicable skill-based protocols need to be evaluated using quantitative outcome measures from instrumental assessments such as VFSS, and neural imaging studies such as MRI. Well-designed treatment studies will provide valuable insight to the neural and biomechanical changes attributed to swallowing skill-training in HD.

Chapter 6. Research Objectives and Hypotheses

6.1 Test-Retest Study: Research Objectives and Hypotheses

Research Question: Literature describing dysphagia associated with HD has used a range of instrumental and clinical measures of swallowing, as described in Chapters 4 and 5. Currently, available research consists predominantly of small cohorts or single case studies using non-standardised assessment measures (Burnip et al., 2019; Heemskerk & Roos, 2011; Pizzorni et al., 2020). The lack of objective measurements of swallowing in this population limits comparison and critical analysis of treatment studies aimed at determining the effectiveness of intervention. There exists a need for further understanding of the reliability of existing methods to evaluate and monitor swallowing in patients with HD. Therefore, the question remains: Which objective swallowing outcome measures have acceptable reliability and stability following a test-retest protocol in individuals with HD?

Primary Objectives:

- To evaluate and quantify the test-retest reliability of swallowing outcome measures over time in a cohort of individuals with HD.
- To evaluate and quantify the variability of swallowing outcome measures by calculating the estimated change across sessions in a test-retest protocol.

Hypotheses:

1. There will be no significant change in any parameters of clinical outcome measures derived from standardised assessments of deglutition over three assessment sessions.
2. Variability will be higher in this patient population compared to available data in healthy adults (Macrae et al., 2011); this variability within and across sessions will be quantified as estimated percent change**.**

Significance: Reliability and validity of each selected outcome measure has previously been reported in healthy people or other aetiologies such as MND and stroke as discussed in Chapter 3 of the literature review. This evaluation of measurement reliability and variability lays the foundation for subsequent research evaluating dysphagia intervention and will inform clinical application of these swallowing outcomes for this neurodegenerative disease. By first systematically evaluating the measurement characteristics of these objective outcomes, measurement error and expected variability for this patient population can be quantified and considered when evaluating treatment effects or planning future studies. Evidence to quantify the estimated variability of swallowing outcomes in healthy participants is only available for LRM outcome measures (Macrae et al., 2011), therefore our results will be compared to this maximum estimated change. This study is clinically significant by contributing to research and understanding of dysphagia in this population using several objective methods of swallowing evaluation.

Proposed Study: Participants with a diagnosis of HD and dysphagia will complete three assessment sessions over one week. No other treatment or changes in medication regimes will occur over this week. Estimated percent change, intra-rater, inter-rater, and test-retest reliability of all outcome measures will be calculated across sessions as described in Chapter 7.

6.2 Treatment Study: Research Objectives and Hypotheses

Research Question: Dysphagia management in HD is primarily based on compensatory approaches (Heemskerk & Roos, 2011; Kagel & Leopold, 1992) and two recent reviews have highlighted that literature investigating rehabilitative interventions to maintain or improve this highly prevalent symptom were lacking (Burnip et al., 2019; Pizzorni et al., 2020). As summarised in Chapter 5, preliminary research has shown beneficial effects of skill-based

approaches to dysphagia rehabilitation in other neurodegenerative aetiologies. There is, however, a lack of pre-existing data on which to base the hypotheses of this treatment study. This study has therefore included a wide range of swallowing outcome measures (as summarised in Table 6.1) to fully explore which aspects of swallowing may be more amenable to change following skill-based swallowing training in HD. Therefore, the following research questions exist:

- Feasibility: Is daily skill-based swallowing training feasible without any adverse effects such as perceived deterioration in swallowing function in individuals with HD?
- Physiological Impact: Is skill-based swallowing training effective in maintaining or improving swallowing safety or biomechanics in individuals with HD?
- Patient Reported QoL: Is skill-based swallowing training effective in maintaining or improving patient reported swallowing QoL in individuals with HD?
- Maintenance: Will the effects of the skill-based swallowing training be retained following two weeks of non-treatment?

Primary Objectives:

- To determine the impact of a two-week skill based swallowing training on functional and instrumental swallowing outcomes detailed in Table 6.1.
- To determine if any changes in swallowing outcome measures were maintained two week post-training.

Hypotheses*:*

1. Intensive skill-based intervention will significantly improve swallowing safety and efficiency in individuals with dysphagia associated with HD. This will be measured by a significant improvement in one or more clinical measures of deglutition as indicated

in Table 6.1. This intervention aims to improve the overall safety and efficiency of the swallowing motor response. This improved efficiency may be reflected differently in timing or displacement measures of swallowing biomechanics, therefore the direction of change for each outcome cannot be specified. Functional outcome measures such as swallowing capacity and volume acquired using the TWST would be expected to significantly improve (closer to normative values). As previously discussed in Sections 4.2.3 to 4.2.6 some studies have reported altered bolus transit times or reduced hyoid movement in individuals with HD, but there is insufficient information to be able to clearly define the direction of change anticipated as this will be dependent on the group characteristics.

2. There will be no significant deterioration in functional swallowing as measured by the clinical and instrumental outcome measures listed in Table 6.1 after a two-week retention period post-therapy.
3. The rate of change will be significantly greater during the treatment period compared to the baseline control period. The rate of change will be calculated across assessments for all swallowing outcome measures detailed in Table 6.1.
4. Swallowing biomechanics will be executed with significantly less variability post-therapy. This will be indicated by a significant reduction in within-session variability of one or more of the swallowing outcome measures detailed in Table 6.1 when comparing across baseline, treatment and maintenance time points.

Table 6.1

Summary of Swallowing Outcome Measures

	Assessment	Outcome measures	Hypothesised direction of change pre/post-treatment
1	Timed Water Swallowing Test (TWST)	Swallow volume (mls/swallow)	↑
		Swallow capacity (mls/sec)	↑
		Time per swallow (s/swallows)	↓
2	Test of Masticating and Swallowing Solids (TOMASS)	Number of bites	~
		Number of masticatory cycles	~
		Number of swallows	~
		Total time (s)	↓
3	Videofluoroscopy swallowing study with low-resolution manometry (Manofluoroscopy)	Oral transit time (s)	~
		Pharyngeal transit time (s)	~
		Total transit time (s)	~
		Timing of supraglottic closure (s)	↑
		Duration of UES opening (s)	↑
		Duration of aryepiglottic closure (s)	↑
		Maximum UES distension (mm)	~
		Hyoid displacement (mm)	~
		Pharyngeal constriction ratio	↓
		Peak amplitude of sensor 1(mmHg)	~
		Peak amplitude of sensor 2 (mmHg)	~
		Duration between peak amplitudes of sensor 1 and sensor 2 (s)	↓
		Minimum pressure of sensor 3 (mmHg)	~
		Duration of UES opening (s)	↑
		Penetration-Aspiration Scale	↓
4	Ultrasound	Hyoid displacement (percent change hyoid-mandible approximation)	↑
		Hyoid rest	*
		Hyoid maximum displacement	*
		Cross sectional area of the submental muscles: left and right anterior belly of the digastric muscles, and geniohyoid^{+} muscles (mm^2)	~

5	Swallowing Quality of Life Questionnaire (SWAL-QoL)	Oral symptoms	~
		Pharyngeal symptoms	↑
		Secretions	↑
		Total impact	↑

Note. * Represents outcome measures only evaluated in the test-retest study.

~ Represents outcome measures where the direction of change is dependent on initial results and a definitive hypothesis cannot be determined (i.e. the baseline number of bites as measured by the TOMASS may be higher or lower than normative data in patients with HD, the oral transit time has been reported as shorter and longer than matched norms in HD associated with tachyphagia observed with hyperkinetic motor symptoms or delayed initiation observed with hypokinetic motor impairments) or the outcome is not expected to change with this skill-based therapy.

Significance: This treatment study will contribute to developing research focused on skill-based dysphagia training. The feasibility and effectiveness of dysphagia rehabilitation in HD is poorly understood at present; however, any changes in swallowing biomechanics in this neurodegenerative disease could be clinically significant. If intensive rehabilitation is effective in improving the safety and efficiency of swallowing, this could reduce the risk of aspiration and subsequent respiratory complications. Increased conscious control or awareness of eating and drinking as a result of dysphagia rehabilitation could improve pre-oral phase impairments such as reduced insight or tachyphagia in HD. An understanding of which features of swallowing may be amenable to treatment in HD would be beneficial to guide future research designs. If treatment effects are maintained after cessation of treatment, this could provide evidence that swallowing function can be maintained and rehabilitation could slow symptom progression in this neurodegenerative disease.

Proposed Study: For this exploratory research, a within-subjects A-B-A study design will compare swallowing outcome measures pre- and post- a two week no treatment period to assess baseline performance. The same measures will then be compared pre- and post- two weeks of daily skill-based dysphagia rehabilitation to evaluate treatment effect. This design will compare swallowing outcome measures pre- and post- an additional two-week period of no treatment post-therapy to evaluate maintenance of treatment effects. This treatment study aims to evaluate three types of changes, namely the average change in raw data pre- and post-training in the swallowing outcome measures listed in Table 6.1, the average change in variability of these outcomes and the difference in the pattern of change between baseline, treatment and maintenance time periods to evaluate any treatment effect in individuals with HD.

Chapter 7: Methods of Test-Retest Reliability Study and Treatment Study

7.1 Test-retest Reliability Study Design

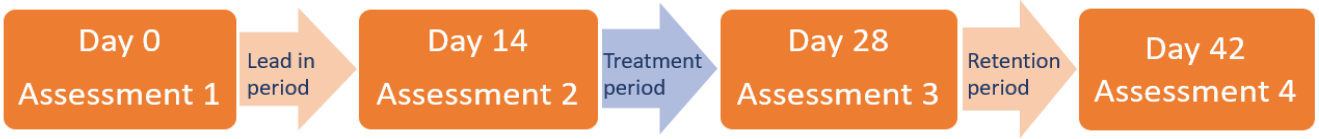
To evaluate reliability and variability of swallowing outcome measurement, a within-subject, repeated measures study design was utilised. Participants were assessed on three occasions over one week (Monday / Wednesday / Friday). To ensure consistency, session times and assessment protocols were consistent within subjects. Medication regimes were unchanged during the study as reported by each participant.

7.2 Treatment Study Design

The treatment study utilised an A-B-A design as summarised in Figure 7.1. This included two phases of 'no-treatment' as controls in order to monitor participant's baseline prior to intervention and assess the maintenance of any treatment effects. Swallowing outcome measures were taken during four assessment sessions, all separated by two weeks. Assessment 1 and 2 were separated by two weeks of no intervention which represented the lead in period. The treatment period was two weeks between Assessment 2 and 3 consisted of daily skill-based dysphagia therapy. Assessment 3 and 4 were then separated by two weeks of no treatment which denoted the maintenance period.

Figure 7.1

Timeline of Assessment and Treatment



7.3 Participants and Recruitment

The inclusion and exclusion criteria for both the test-retest and the treatment studies were identical. Participants were included if they were > 30 years, (to ensure participants did not have juvenile disease) with a diagnosis of HD through clinical symptoms confirmed by a neurologist and the presence of ≥ 36 CAG repeats on genetic testing. Participants were judged by the referring medical professional (General Practitioner or HD Coordinator) to have adequate cognitive-communication function to provide informed consent; this was ensured by having the referrer submit a 'Capacity to Consent' form (see Appendix D). Once this form was received from the referring professional and with consent, the primary investigator contacted the participant to provide further details about the projects and asked if they were interested in a screening appointment.

Participants were screened to exclude those who were not suitable for these studies. Firstly, the presence of dysphagia was screened using the validated EAT-10questionnaire. This ten-item self-reported tool is a valid and reliable short screening assessment for dysphagia that incorporates both physiological and psycho-social domains of swallowing (Belafsky et al., 2008). This questionnaire was completed with the investigator during the initial screening appointment. Participants rated their symptoms on a five-point scale, providing a total score out of 40. A score of three or higher is indicative of swallowing problems in patient populations. In a similar neurodegenerative disease (MND), EAT-10 screening sensitivity of 88% and specificity of 57% was reported for predicting dysphagia in those who demonstrated penetration or aspiration on instrumental assessment (Belafsky et al., 2008; Plowman et al., 2016). Participants were included if they scored ≥ 3 indicating swallowing impairment as perceived by the individual, and oral intake was their main source of nutrition and hydration.

Secondly, the Montreal Cognitive Assessment (MoCA) was completed during the screening appointment. The MoCA is the most sensitive cognitive screening tool for individuals with HD (Mickes et al., 2010). The purpose of the MoCA was to quantify baseline level of cognition as part of the participant demographic information and was not repeated or recorded as an outcome measure. The assessment consisted of questions and activities, scored out of 30; a score of > 26 indicated normal cognition (Nasreddine et al., 2005). Begetietal et al. (2013) reported that mild cognitive impairments were found across all stages of HD. Thus, investigators were cautious to impose a specific cut-off based on the MoCA as patients may be limited by other factors such as motor impairment affecting dexterity or communication in later stages of HD. The main inclusion criteria for both studies was 'adequate' cognition to provide informed consent. In other neurodegenerative aetiologies, a score of ≥ 17 on the MoCA was identified as sensitive cut-off to detect between mild cognitive impairment and dementia (Trzepacz et al., 2015). MoCA performance during screening provided information regarding the participant's ability to follow verbal instructions, attention, visual-spatial abilities and processing time. Therefore, participants were excluded if they lacked sufficient cognition to attempt all sections of the MoCA.

Demographic information was collected prior to the initial assessment session. Participants and their families provided information regarding their medication and number of years they have been symptomatic. Participants were asked not to change their medication regime or take part in any other research trials during this research programme. When available, the stage of the disease was quantified using the Unified Huntington's Disease Rating Scale (UHDRS), an internationally recognised clinical rating scale used in many studies to measure four key domains: motor impairment, cognition, functional ability and behavioural impairment (Mariscal et al., 2014). Where this information was not available, disease staging was judged

with the referring professional using the Shoulson-Fahn staging scale (Shoulson & Fahn, 1979). All disease stages were included if they met the inclusion criteria.

Potential participants were given a full explanation of the protocols and the corresponding information sheet (see Appendix B and C) by the primary researcher. They were informed that they could withdraw from the study at any time. Participants were given the opportunity to ask questions and talk to their family before they agreed to take part.

7.4 Ethical Considerations

The test-retest study received national Health and Disability Ethics Committee approval: 18/CEN/20/AM01. The treatment study received national Health and Disability Ethics Committee approval in December 2107. An amendment was submitted in August 2018 to extend data collection to include home visits and improve recruitment and accessibility of intervention. This was approved in October 2018 (17/NTB/214/AM02). All participants provided informed consent and demonstrated capacity to follow verbal instructions.

7.5 Procedures

All data collection for the test-retest study was completed by the same investigator in a specialised university swallowing research laboratory using the same equipment and procedures for all participants. The order of assessments remained consistent for all participants across all three sessions. For the treatment study, participants from Christchurch attended all assessment sessions at the Rose Centre for Stroke Recovery and Research. Auckland participants attended VFSS appointments as part of an outpatient radiology clinic at North Shore Hospital; all other assessment procedures either took place in a clinical room during the

hospital visit or at the participant's home within two hours of the VFSS. All procedures were carried out by the same two researchers who had trained as Speech and Language Therapists.

7.6 Materials and Instrumentation

7.6.1 Assessment Instrumentation

The protocol for each swallowing assessment was consistent for all participants across both studies; however, the treatment study equipment varied between Christchurch and Auckland localities due to resource availability. In Christchurch, videofluoroscopic data were recorded at 25 fps with low dose continuous screening using a GE Healthcare – OEC FluoroStar 7900 series scanner. Videos were exported directly from the FluoroStar to a USB device. Manometric data were collected using a bridge amplifier connected to an 8 - channel PowerLab system (Quad Bridge Amp FE224; PowerLab 8/35, ADInstruments Pty Ltd, Bella Vista, NSW, Australia) with a maximum sampling rate of 100 kHz using four inputs. A Gaeltec manometric catheter, (Model CTS3, Gaeltec, Hackensack, NJ, USA) 100 cm long and 2.1 mm in diameter contained three uni-directional, posteriorly oriented sensors as per standardised catheter recommendations (Salassa et al., 1998). Sensor 1 and 2 were distributed 20 mm apart. Sensors 2 and 3 were separated by 30 mm. These data were analysed offline using commercially available software (ADI LabChart Pro software version 8.1.13). VFSS data were transferred in real time to the computer using a SVID2USB2 USB 2.0 S-Video/Composite video Capture Cable to USB device and visualized in LabChart using the Video Capture module. Manometric and VFSS data were synchronized in LabChart using a custom-made foot pedal trigger which allowed researchers to close an electronic circuit to begin simultaneous VFSS recording on the FluoroStar and video capture on LabChart. Synchronization was confirmed using a visual indication of the trigger completing the circuit on Channel 4 of LabChart software.

High-resolution US images were collected using a Sonosite X-PORTE Ultrasound system (FUJIFILM SonoSite, Inc, Bothell, USA). Assessment utilised both the curvilinear transducer (C60xp 5-2 MHz, with custom exam settings based on abdominal exam type, depth: 7cm - 30 cm) and the linear transducer (HFL50xp 15-6 MHz, with custom exam settings based on musculoskeletal exam type, depth: 4cm - 6 cm) as pictured in Figure 9. Images were visualised on a 19 inch (48.2 cm) monitor.

Figure 7.2

Visual Representation of the Sonosite X-PORTE Ultrasound Transducers

In Auckland, LRM data were not collected as the equipment was not available. VFSS data were captured using a Toshiba Ultimax Fluoroscopy unit in low dose continuous screening mode. Digital images were recorded at 30 fps using a Medi-capture USB 170 recorder (USB 170 Medicap). These videos were saved on a password protected USB device to comply with hospital confidentiality standards and then de-identified when downloaded for analysis.

US images were collected using the portable Clarius^{TM} curvilinear (C3; frequency range: 2 - 6 MHz, abdominal exam type, depth: 3 - 30 cm) and linear (L7; frequency range: 4 - 13 MHz, breast exam type, depth: 1 - 7 cm) transducers pictured in Figure 7.3 (Clarius, Burnaby, British Columbia, Canada). The transducers connected wirelessly to the Clarius^{TM} application software installed on an iPad. Videos were visualised and recorded on the iPad 9.7 inch (25 cm) display at 20 fps. Saved recordings were exported when connected to WIFI to the secure Clarius^{TM} online cloud. After each assessment session, the investigator downloaded the recordings directly from the cloud for subsequent analyses.

Figure 7.3

Visual Representation of the Clarius^{TM} Curvilinear and Linear Transducers

7.6.2 Intervention Instrumentation

The training protocol utilised a portable sEMG Verity Medical Myotrac Simplex Plus device (v1.4-4, NeuroTrac® Simplex, Verity Ltd., UK). Three snap-style 10 mm silver chloride

electrodes, backed with nickel plated brass snaps implanted within a single use self-adhesive foam patch (50.8 mm diameter, T3402 sEMG Round Triode^{TM} Electrode, Thought Technology Ltd., Canada) were adhered to the participant's skin. The three electrodes (two recording and one ground) were equidistant. These signals were transmitted via Bluetooth to a HP laptop computer (48 cm display) and the custom designed Biofeedback in Strength and Skill Training (BiSSkiT) software (Huckabee, Sella, Jones & Han). One participant completed the training in the laboratory setting on a desktop computer (56 cm display). Participant data files were saved using non-identifiable study code and exported as a Microsoft Excel Comma Separated Values File (.csv).

7.7 Assessment Sessions

Assessment sessions for both studies consisted of four assessment procedures; two participants underwent additional MRI during the treatment study. The Swallowing Quality of Life Questionnaire (SWAL-QoL) was completed during each assessment as part of the treatment study only. All assessment sessions were conducted by the same two investigators who were trained Speech and Language Therapists and researchers within the same laboratory. The primary investigator had six years of clinical experience including dysphagia assessment and diagnosis. The second investigator had four years of experience in dysphagia assessment and diagnosis. Investigators were trained and completed competencies in all instrumental procedures for at least twelve months before data collection. Assessment protocols were developed and refined during group meetings prior to data collection. No formal assessment of rater calibration, agreement, or minimal level of reliability of measurements was conducted prior to data analysis. All swallowing outcome measures are summarised in Table 6.1 (p. 124).

7.7.1 Timed Water Swallowing Test

As discussed in Chapter 3, the TWST assessed the participant's functional ability to consume liquid (Hughes & Wiles, 1996). The TWST requires participants to drink 150 mls of room temperature water "as quickly as is comfortably possible". Each participant was video recorded using a video camera or iPad positioned under the chin and to the side to visualise movement of the thyroid cartilage. The investigator recorded the time taken in seconds for the patient to consume the water from the moment the cup touched their lips until the larynx returned to rest after the final swallow (Hughes & Wiles, 1996). The number of swallows were also recorded. In the reliability study, these outcomes were recorded by the investigator during the assessment. To allow for blinding of session during the treatment study, data were not extracted online. Each recording across participants and assessments was assigned a randomised number by a third researcher. The investigator then reviewed these video recordings offline to quantify number of swallows and time taken for the patient to consume the water. Three quantitative parameters were obtained from these data: swallowing capacity (mls / s), average volume per swallow (mls / number of swallows) and average time per swallow (total time in seconds / number of swallows). Video recordings were used for offline intra-rater and inter-rater measurements in both studies. All participants were able and willing to attempt the task in all assessment sessions. The TWST was discontinued if the task was judged by the researcher to be unsafe, such as significant evidence of coughing or vocal changes during the assessment. If this occurred, any remaining water was measured and subtracted from the 150 mls for subsequent analysis.

7.7.2 The Test of Masticating and Swallowing Solids (TOMASS)

The TOMASS is a valid, reliable measure of masticatory and swallowing efficiency of a solid bolus, with published normative data (Huckabee et al., 2017). Participants were asked to eat

one Arnott's SALADA^{TM} cracker "as quickly as is comfortably possible" and say their name when they finished. A video recording was taken as described in the TWST above. For the reliability study, the number of discrete bites, swallows, masticatory cycles and the time taken for a participant to consume a cracker were collected by the investigator during the assessment. For the treatment study, each video was assigned a randomised number during blinding and reviewed by the investigator offline to extract the same four outcomes. As some participants avoided harder textures or typically had 'soft' diets, the assessment was deferred if it was deemed unsafe by the researcher based on diet history, discussion with the participant or observed behaviour.

7.7.3 Videofluoroscopy and Manometry (Manofluoroscopy)

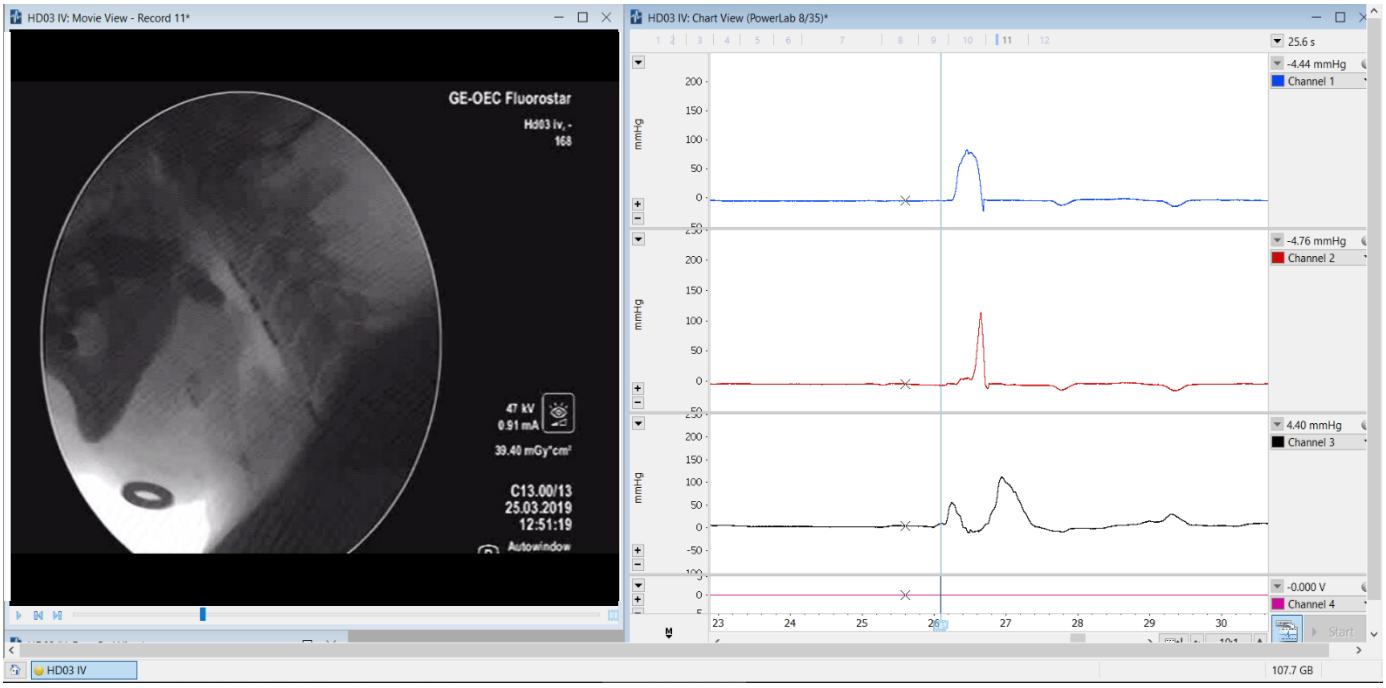
Videofluoroscopic Swallowing Studies (VFSS) were a key instrumental tool to evaluate bolus transit and any changes in swallowing biomechanics during this treatment study. Participants in Christchurch who completed the test-retest study and treatment study underwent videofluoroscopy in conjunction with LRM (manofluoroscopy). Participants in Auckland did not undergo manometric assessment as this equipment was not available in this location. Identical assessment protocols were completed for VFSS measurements without the manometric catheter in situ.

Participants were seated in a high-backed chair or personalised wheelchair with head rest support to avoid neck hyperextension associated with choreic movements. In the lateral view, the participant was seated comfortably within the videofluoroscopy planes. The target radiographic field included the lips anteriorly, the cervical spine posteriorly, the posterior nasal spine superiorly and the cervical oesophagus inferiorly in the lateral view (Leonard, 2019a). A radio-opaque coin, 20 mm in diameter, was placed under the participant's chin using medical

tape and used for post-hoc calibration measurement of spatial parameters. A Gaeltec manometric catheter contained three uni-directional, posteriorly oriented sensors as per standardised catheter recommendations (Salassa et al., 1998). Nasal anaesthetic was not used as this may impact on swallowing magnitude during dry and liquid swallows (Guiu Hernandez et al., 2018). The ovoid catheter was inserted through the nares and into the pharynx; it was guided into the proximal oesophagus by the participant swallowing water through a straw. Correct placement was indicated by typical 'M waves' visible at Sensor 3 during swallowing events (Castell & Castell, 1993). Additionally, accurate placement was evaluated radiographically and unidirectional markers on the catheter were checked when the catheter was securely taped in position to ensure posterior orientation during the study. When correctly placed, Sensor 1 was situated in the proximal pharynx, Sensor 2 in the distal pharynx and Sensor 3 in the proximal aspect of the UES. The number of unidirectional markers was also noted when placement was confirmed for each participant to ensure consistency across sessions. Figure 7.4 provides an example of one swallowing event captured with LRM and simultaneous VFSS.

Figure 7.4

Example of LRM Data Collection with Simultaneous VFSS Reviewed Using ADI LabChart Pro Software



Each participant was positioned according to a standardized protocol of VFSS and asked to hold a 1 ml bolus to acquire a baseline 'hold position' as a reference for subsequent calculations (Leonard, 2019a). The following conditions were administered: three dry/saliva swallows, three 5 ml water boluses (International Dysphagia Diet Standardisation Initiative (IDDSI) Level 0) and three 5 ml liquidised boluses (Watties® apple puree; IDDSI Level 3) (Cichero et al., 2017). This bolus volume was selected for consistency of swallowing response across US, VFSS and LRM assessments and to allow for comparison of reliability and measures across studies. Previous research in HD reported that larger volumes such as 20 ml required multiple oral intake events making comparison between trials problematic (Hamakawa et al., 2004). Compared to a much smaller bolus (1 ml or 3 ml), 5 ml has been shown to be an adequate size to evaluate swallowing safety and biomechanics in HD (Hamakawa et al., 2004; Woisard et

al., 2020). Boluses were prepared with X-Opaque HD Barium Sulfate powder (30% w/y concentration) and mixed immediately prior to presentation to ensure equal distribution of barium sulfate. All 5 ml boluses were measured using a 5 ml or 10 ml syringe. Water boluses were offered in a 20 ml plastic medicine cup and puree boluses via a plastic spoon. Participants were encouraged to self-feed where possible for consistency of responses; however, hand over hand assistance was provided if requested. Dry swallows were elicited using a verbal and visual countdown to minimise radiographic screening time. Participants verbally indicated when they had sufficient saliva for a dry swallow. The investigator standing more than one metre away counted "three, two, one swallow" and screening began. Screening was stopped when the larynx returned to rest position after the swallowing event. Each VFSS trial was limited to a maximum 30 s of screening as pre-determined by the hardware set-up. The time between swallowing trials varied from 30 to 60 s. This was dependent on the time to replenish saliva for dry swallows and time taken for the previous video to be saved. Each trial was labelled on LabChart as 'Dry', 'Water' or 'Puree'. All manofluoroscopy measurements were digitally recorded for subsequent analysis in the test-retest study. These digital recordings were coded by a third researcher for blinded data extraction during the treatment study.

7.7.3.1 Videofluoroscopic Measurement Techniques

All videofluoroscopic data were exported from the Fluorostar using a USB flash drive (Christchurch) or Medi-capture USB 170 (Auckland) recorder. For the treatment study, each data file was assigned a randomised number by a third researcher during the blinding process. QuickTime Player (Version 7.7.9, Apple Inc.) was used to review the videos frame-by-frame and select images. A Microsoft® Surface Pro 3, 12 inch tablet computer with 2160 x 1440 multi-touch screen was used with the Microsoft® Surface stylus pen for accurate two-dimensional measurement of the area of the pharynx in the measurement software.

Measurements were obtained using ImageJ (U.S. National Institutes of Health, Bethesda, Maryland, USA) and GNU Image Manipulation Program (2.10.10) software. All measurements obtained via manofluoroscopy are summarised in Table 6.1 (p.119). A total of six timing measurements were calculated for each water and puree swallowing event. To extract the data, each video was opened in QuickTime player, the 'Movie Inspector' window within QuickTime Player was also opened to provide accurate timing information in milliseconds. The investigator scrolled through each video to identify the target swallowing event. If videos contained multiple swallows for one bolus, the swallow which was judged by the investigator to contain the largest bolus volume was selected for measurement; this was typically the first swallow. If it was unclear which contained the largest bolus, then the first swallow was selected. All measurements were made using the techniques described by Leonard (2019a), and defined as:

- Oral transit time: time from the head of the bolus passing the posterior nasal spine during initiation of the swallowing event (B1) to the time the bolus head reached the base of the vallecula (BV1).
- Pharyngeal transit time: time from the bolus head exiting the vallecula space (BV2) to the time the bolus tail cleared through the UES (BP2).
- Total transit time: oral and pharyngeal transit time combined.
- Timing of supraglottic closure: time of the maximum completion of supraglottic closure; the moment the arytenoid cartridges made maximum contact with the inferior aspect of the deflected epiglottis (AEclose) minus the timing of the bolus head when it entered the UES (BP1).
- Duration of aryepiglottic closure: timing of the maximum completion of supraglottic closure (AEclose) to the time the epiglottis returned to the upright rest position (EM).

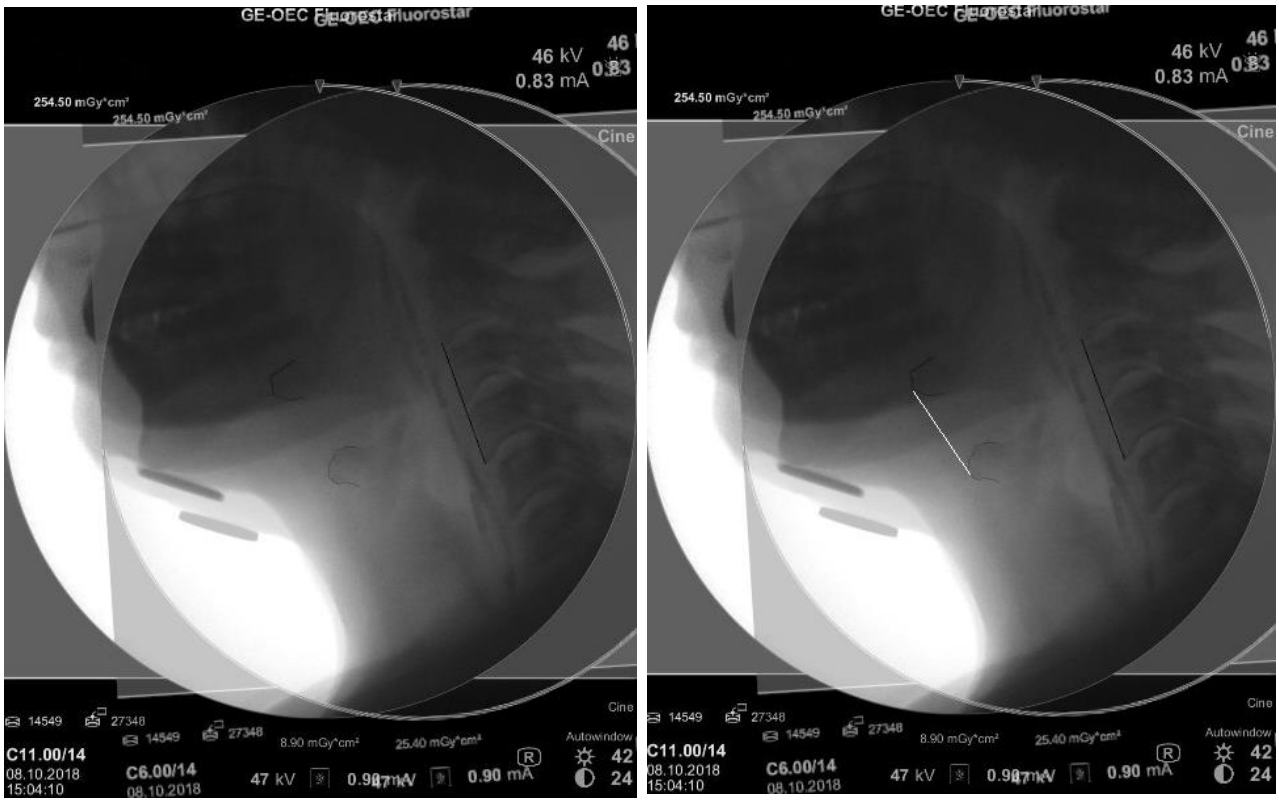
- UES opening duration: time the bolus head first entered the UES (BP1) to the time the tail of the bolus exited the UES (BP2).

Swallowing gestures included hyoid displacement, pharyngeal constriction ratio (PCR) and UES distention. Hyoid displacement was calculated using still images acquired from each trial video. The same computer was used to acquire screenshots during image selection to ensure number of pixels and orientation of images were consistent. Using QuickTime Player, the investigator scrolled frame-by-frame to identify the image of maximum anterior and superior hyoid displacement during the swallowing event. The image was saved as 'hyoid max'. The rest position was obtained using the 1 ml bolus hold video, again the video was reviewed to select the frame representing the 'hyoid rest' position. Both the rest and maximum images were opened in GNU Image Manipulation Program software. Using the drawing tool (1 pixel at 100%), a line was drawn from inferior anterior border of cervical spine 2 (C2) to the superior anterior border of cervical spine 4 (C4). The anterior, inferior portion of the hyoid was also drawn in the two images. The images were then overlaid, and the opacity of the hyoid max image was reduced to 50% to allow for alignment of cervical vertebra using the C2 to C4 lines so that a single vertebral column is visible. This overlaid image was exported as a high-quality JPEG to ImageJ software. A radio-opaque coin was used for calibration and the distance between the most anterior, inferior portion of the hyoid was measured between the rest and maximum positions. An example of this measurement is depicted in Figure 7.5.

Figure 7.5

Representation of Hyoid Displacement Measurement from VFSS

(a) (b)



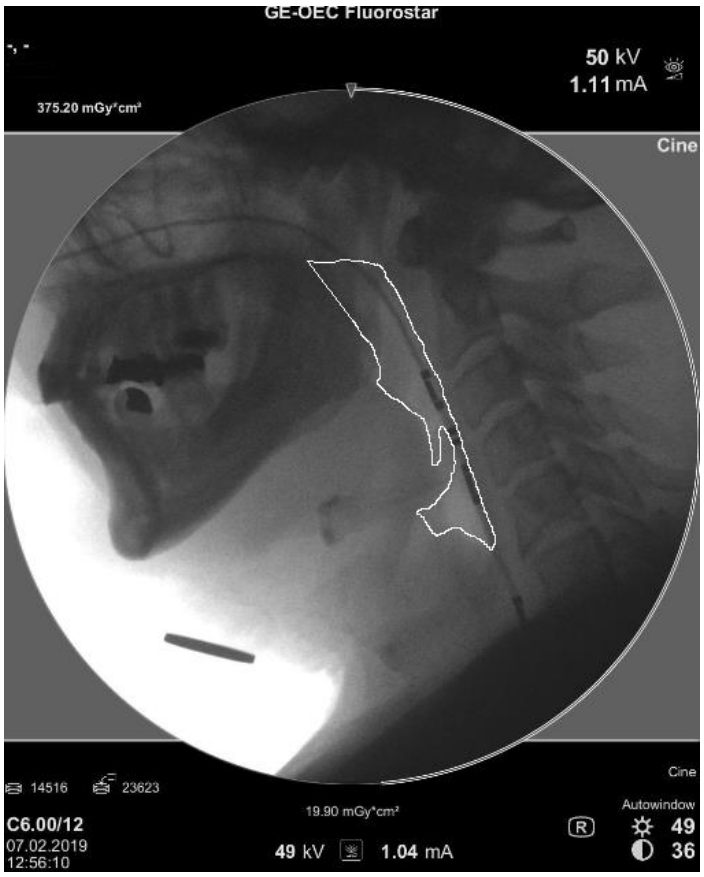
Note. Image 7.5a depicts two overlaid images of the hyoid at rest and hyoid at maximum displacement during swallowing. Image 7.5b demonstrates measurement of the distance between the hyoid at rest and hyoid at maximum displacement during swallowing.

This 1 ml bolus hold was initially collected as a still image for the first five participants included in the test-test study; however, a difference in formatting was identified between still images and video files saved with the Fluorostar device. The still images required adjustment using GNU Image Manipulation Program software to ensure images were the same size and could be overlaid. For consistency of methods, to remove additional steps of image processing and to allow for quicker comparison of data, video files were recorded for all trials including the 1 ml bolus hold from participant six onwards. Pharyngeal constriction ration (PCR) was calculated using the 1 ml bolus hold screenshot to measure the two-dimensional area of the

pharynx at rest. The ‘rest’ image was transferred onto a Microsoft® Surface tablet and opened in ImageJ software. The radio-opaque coin was used for calibration, then a Microsoft® Surface stylus pen was utilised for best accuracy as the pharynx was outlined. The investigator started drawing from the posterior nasal spine tracing across to the centre of the tubercle of the atlas. The posterior pharyngeal wall was followed inferiorly to the visible portion of the pyriform sinus. The investigator then traced over the arytenoid cartilage across to the internal surface of the epiglottis at the point of connection to the thyroepiglottic ligament. It was then traced around the epiglottis structure, into the valleculae where visible, around the BoT and around the soft palate if visible. If the contour of the soft palate was not visible, the line was connected directly to the starting point at the posterior nasal spine. Care was taken not to pass anteriorly to the posterior nasal spine as this would not be included in the area of the pharynx. Once the investigator was satisfied with the outlined pharynx, the area was measured in mm^2. An example of this measurement is provided in Figure 7.6.

Figure 7.6

Measurement of the Two-dimensional Area of the Pharynx at Rest



This method varied slightly from that described by Leonard (2019a). The authors described drawing around the shadow of the arytenoid cartilages, not entering the laryngeal vestibule but drawing horizontally to meet the laryngeal surface of the epiglottis. During investigator training sessions and consensus meetings, there was no clear rule of an anatomical point to meet on the laryngeal surface of the epiglottis. Therefore, for consistency, the decision was made to identify a specific part of the internal surface of the epiglottis as described above. The second part of PCR measurement required an image of the pharynx at maximal constriction. This was typically seen at the point of maximum hyoid excursion; however, the investigator reviewed each video frame-by-frame for accurate image selection. Any residual bolus visible at the time of maximal pharyngeal constriction was measured. The selected image was transferred to the Microsoft® Surface tablet, the image was calibrated, and the visible residue was outlined to

obtain an area in mm^2 shown in Figure 7.7. PCR was calculated using the pharyngeal area at rest compared to any visible air or bolus contrast during maximum constriction: PCR = area at maximum constriction / area in rest position. If no visible residue was present, then the PCR was 0. Values of greater than 25 mm^2 indicate incomplete pharyngeal constriction and up to six times higher risk of aspiration (Kendall & Leonard, 2001).

Figure 7.7

Measurement of the Visible Residual Present During Maximum Pharyngeal Constriction

Finally, UES distension was measured at the point the UES achieved maximum opening. Frame-by-frame scrolling helped the investigator to identify the location of the UES and the videoframe of maximum opening. The screenshot of the selected frame for a swallowing event with a bolus was opened in ImageJ. The radio-opaque coin was used to calibrate for each

swallow. A line was drawn between the narrowest visible point of the UES lumen as represented in Figure 7.8. This was typically identified between cervical spine 4 and 6. The length of this line was recorded in mm.

Figure 7.8

Measurement of the Maximum UES Distention (mm)

In the treatment study, one additional measure of swallowing safety was extracted for each bolus trial as measured via VFSS. The Penetration-Aspiration Scale is a valid and reliable 1-8 scale which provides quantification of events of material entering the airway and any attempts to eject from the airway as observed on videofluoroscopy (Rosenbek et al., 1996a). Each swallowing trial with a bolus was reviewed frame-by frame by the investigator and assigned a PAS rating. Each rating for each bolus trial was included in the analysis. The criteria for this rating is summarised in Table 7.1.

Table 7.1

Penetration-Aspiration Scale Rating Criteria Stipulated by Rosenbek et al. (1996a)

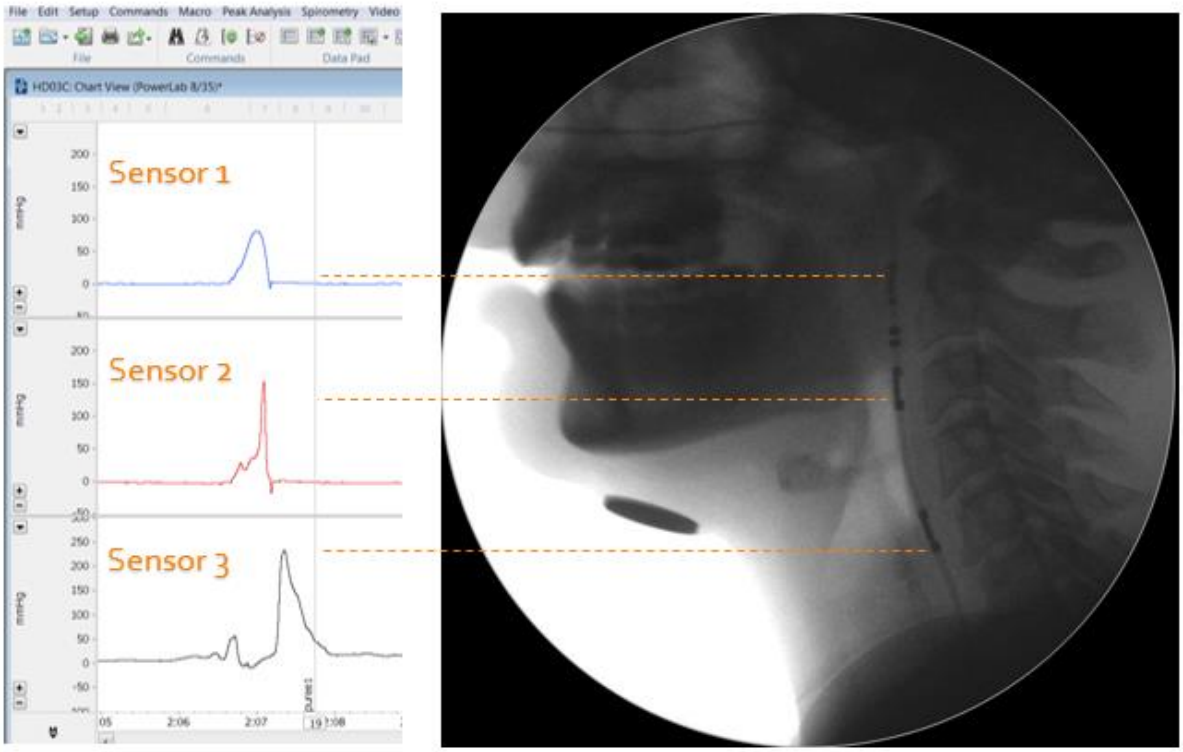
Score	Description of Each Point of the Penetration-Aspiration Scale
1	Material does not enter the airway
2	Material enters the airway, remains above the vocal folds, and is ejected from the airway
3	Material enters the airway, remains above the vocal folds, and is not ejected from the airway
4	Material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

7.7.3.2 Manometric Measurement Techniques

Each trial was identified by an associated text comment ‘Dry1’, ‘Dry2’, ‘Dry3’, ‘Water1’, ‘Water2’, ‘Water3’, ‘Puree1’, ‘Puree2’, or ‘Puree3’ added by the investigator during data collection. The corresponding FluoroStar recordings were reviewed simultaneously to ensure the correct swallowing event had been marked for analysis. All manometric data were extracted using LabChart software. An example of the LabChart data collection window during one swallow with corresponding waveforms at each sensor is presented in Figure 7.9.

Figure 7.9

LabChart Data Collection Window During a Puree Swallow with VFSS Hold Image Representing Position of the Three Sensors



The peak waveforms for Sensor 1 and Sensor 2 were highlighted; the maximum pressure (mmHg) was recorded for each sensor and timing between peaks was recorded in milliseconds. The duration of the UES opening was extracted at Sensor 3. The clearest distinguishable peaks before and after the nadir pressure were highlighted as a characteristic 'M' wave representing the movement and relaxation of the UES during the swallowing event. The timing between these peaks at Sensor 3 and the lowest pressure between these peaks were recorded.

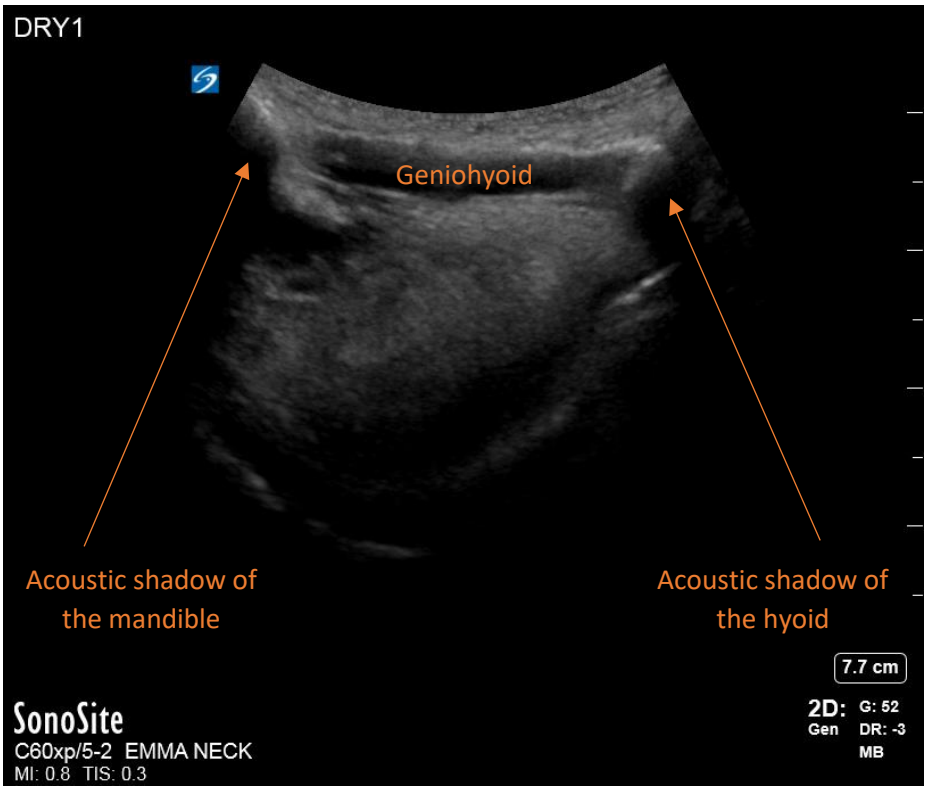
7.7.4 Submental Ultrasonography

US measures were taken using a Sonosite X-PORTE device for all assessments in Christchurch and the portable Clarius^{TM} handheld devices connected to an iPad for participants in Auckland. Seven of the 28 Auckland assessments occurred in the participant's home. Both investigators

completed at least six months of training to practise image acquisition, selection and measurement. Data collection was completed by the same two investigators for both studies. Participants were seated comfortably in a chair or wheelchair with their head in a neutral position. The handheld transducers allowed the researcher to move with the participant in the event of unintentional movement. A curvilinear transducer was coated with a generous amount of aquasonic transmission gel and placed under the chin in a mid-sagittal plane to image hyolaryngeal excursion. The investigator scanned to ensure the acoustic shadow of the mandible was visible anteriorly and the acoustic shadow of the hyoid was visible posteriorly within the scanning window (Figure 7.10). On the Sonosite device, the depth was set at 7.7 cm. Using the Clarius^{TM} device, the depth was between 6.8 cm and 8.8 cm. Manual adjustments such as depth, gain and brightness were made by the investigator during the assessments to aid image quality.

Figure 7.10

Sagittal Sonogram Using a Sonosite X-PORTE Device with Curvilinear Transducer



Note. Image of the acoustic shadow of the mandible anteriorly, the acoustic shadow of the hyoid posteriorly and the geniohyoid muscles from the midline depicting the target window during ultrasonic assessment of hyoid excursion.

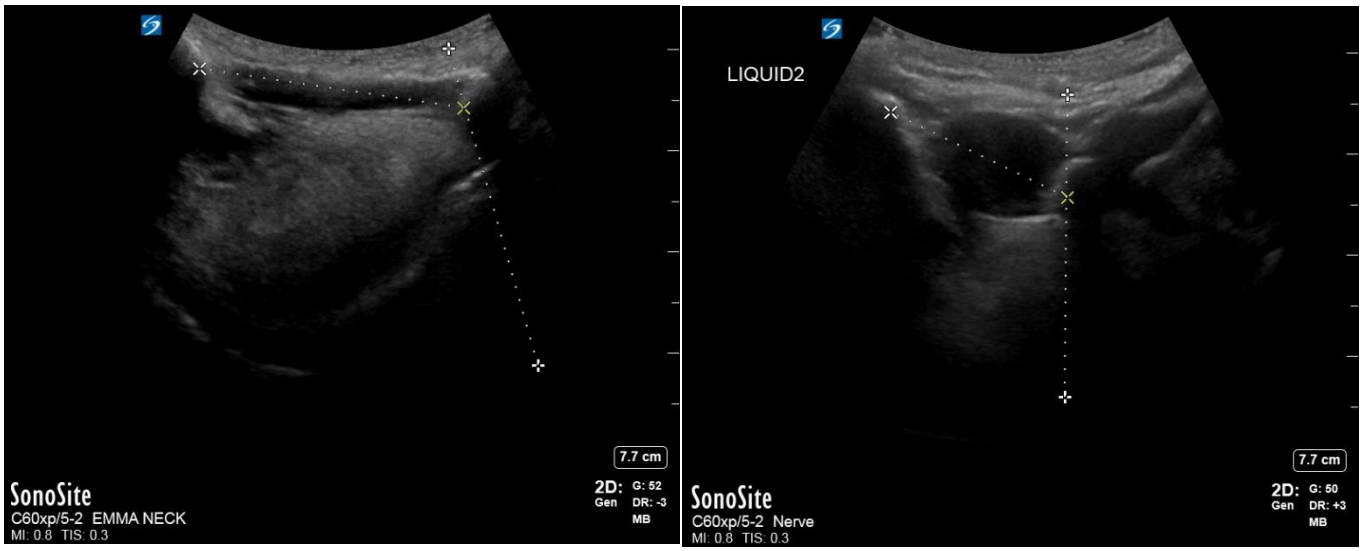
This position was maintained during each swallowing trial. Participants performed three dry/saliva swallows, three 5 ml water bolus trials (IDDSI Level 0) and three 5 ml liquidised bolus trials (Watties® apple puree; IDDSI Level 3). Dry swallows were initiated by instructing the participant to "swallow whenever you are ready". All 5 ml boluses were measured using 5 ml syringes. Measured water and puree boluses were then transferred to a 20 ml plastic medicine cup or to a plastic spoon for ingestion. Participants were encouraged to self-feed where possible for consistency of responses; however, hand over hand assistance was provided if requested. For bolus swallows, the participant was required to hold the bolus in the oral cavity for up to 5 s to allow the investigator to locate the target anatomical reference points in the scanning window. After each trial, scanning was discontinued, and the preceding 30 s of video was automatically saved. The investigator saved each video with the corresponding trial name 'Dry1', 'Dry2', 'Dry3', 'Water1', 'Water2', 'Water3', 'Puree1', 'Puree2', or 'Puree3'. During the assessment and after each trial, the investigator scrolled through the moving image to choose the frame with maximum hyoid displacement, defined as the shortest distance between the two acoustic shadows. The time taken for measurement between trials was typically 1 to 2 minutes depending on how clear the images were to select and measure. The hyoid-at-rest image was selected after the swallowing event to represent the most natural position of the hyoid with no bolus. Participants with involuntary lingual chorea, tongue pumping movements or other extraneous movements were given verbal prompts to relax after the swallow and the investigator continued to scan until the best possible rest position was recorded. All measurements were obtained following a standardised protocol as described by

(Winiker, 2019). Once the target frame was identified, the line measurement tool was selected on the Sonosite X-PORTE Ultrasound device or Clarius^{TM} software on the iPad. Firstly, a line of best fit was drawn along the anterior border of the shadow of the hyoid. A second line was then drawn with one calliper placed on the posterior border of the onset of the shadow of the mandible and one calliper placed at the point of the inferior border of the geniohyoid meeting the line of best fit. The length of this second line in mm was recorded (Figure 7.11). These measurements were taken at rest and maximum excursion and subsequent percentage change was calculated.

Figure 7.11

Images Acquired Using a Sonosite X-PORTE Device with Curvilinear Transducer

(a) (b)



Note. Examples of US measurement of hyoid excursion at rest (a) and maximum displacement (b).

Finally, a linear transducer was placed in the coronal plane to measure the cross-sectional area of two paired submental muscles, specifically the geniohyoid and anterior belly of digastric

muscles, in a rest position with no bolus. The investigator scanned at a depth of 4 to 5 cm with an even pressure anteriorly to posteriorly to find the largest and clearest boundaries for each muscle. The freehand measurement tool within the Sonosite X-PORTE or Clarius^{TM} software was utilised to trace around outside of each muscle and provided measurement of the surface area in mm^2. In the case of the geniohyoid muscles, the right and left geniohyoid muscles meet at midline and the boundary depicting the borders of the geniohyoid and mylohyoid muscles were typically unclear. Therefore, a single measure referred to as 'geniohyoid^{+}' was taken of both muscles together with the superior borders of the mylohyoid muscles included within the surface area of the geniohyoid measurement (Winiker, 2019). One measurement of the paired geniohyoid^{+} muscles, left anterior belly of the digastric and right anterior belly of the digastric area in mm^2 were recorded in each assessment session. Examples of these measurements are shown in Figures 7.12 and 7.13. The US protocol, such as bolus order, was kept consistent across all assessment sessions for both studies.

Figure 7.12

Sonographic Measurement of Geniohyoid^{+} Muscles Taken in the Coronal View Using the Sonosite X-PORTE Device with Linear Transducer

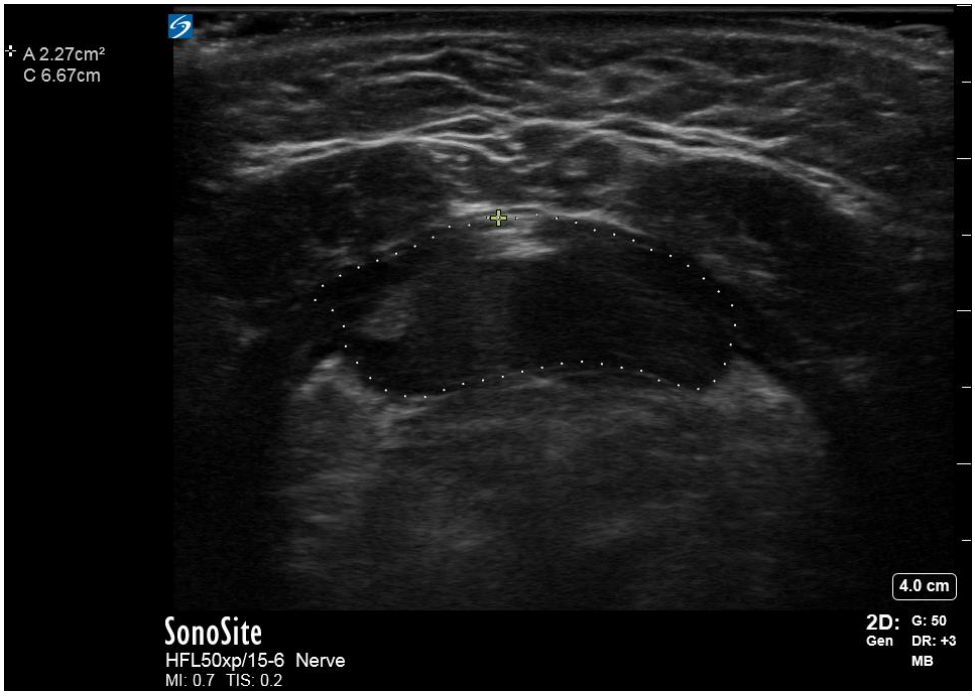
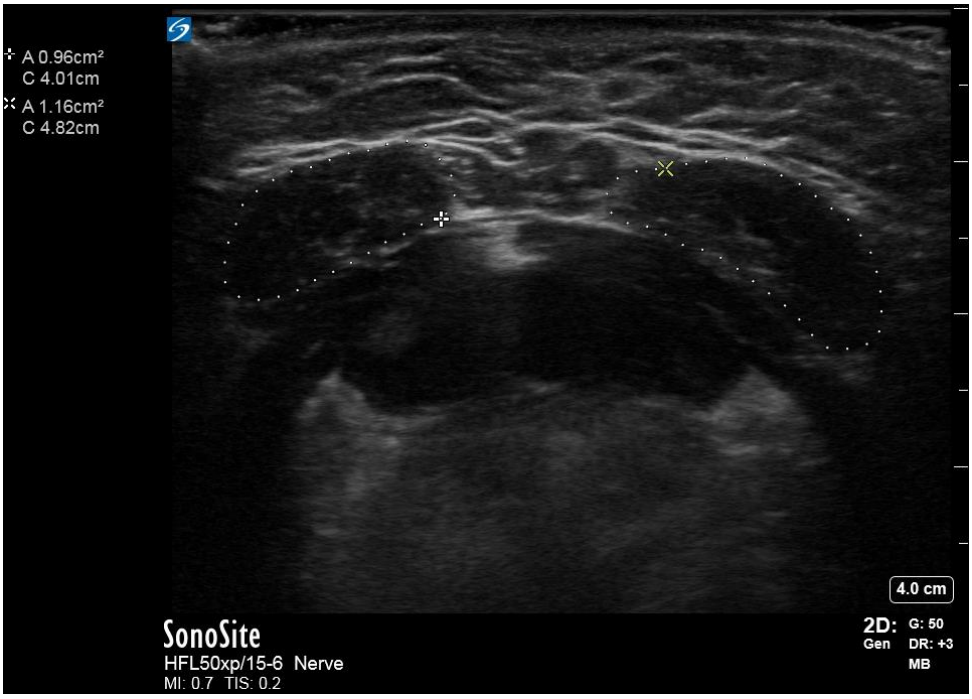


Figure 7.13

Sonographic Measurement of the Left and Right Anterior Belly of the Digastric Muscles Taken in the Coronal View Using the Sonosite X-PORTE Device Linear Transducer



7.7.5 Swallowing Quality of Life Questionnaire (SWAL-QoL)

This questionnaire provided information pertaining to the participant's perception of their swallowing and related QoL factors. It consisted of 44 questions with 10 subsections. Each item was equally weighted, answered with a five-point Likert scale. An overall score out of 100 indicated patient-centred QoL, with decreasing score indicating lowered QoL. Items measuring the severity of dysphagia symptoms were used to calculate four parameters: 'oral symptoms', 'pharyngeal symptoms', 'secretion symptoms ' and 'total symptoms' scaled scores (McHorney et al., 2002). Participants were asked to complete this questionnaire during assessment sessions or complete the questionnaire at home and bring it to the assessment sessions. Participants were given the choice to complete it independently or with support. There are several patient-reported QoL measures specific to swallowing, however, the SWAL-QoL has been reported as the most reliable and valid measure of swallowing related QoL covering

all World Health Organisation International Classification of Functioning areas (Keage et al., 2015). The SWAL-QoL has been utilised in similar projects to evaluate the effectiveness of this skill-based dysphagia training, therefore for replication consistency and comparison across aetiologies, this tool was chosen.

The order and timing of all assessment procedures summarised in Table 6.1 (Chapter 6, p. 119) were kept as consistent as possible, however this was not possible with assessments completed during home visits. This occurred in Auckland due to allocated VFSS timing slots in instances where more than one participant was assessed in the same radiology clinic. The timing and order of assessments differed as the first participant completed the SWAL-QoL, TWST, TOMASS and US before the VFSS outpatient appointment, the second participant required home assessments later that day and the third participant completed these assessments after their VFSS appointment. This discrepancy could have introduced a potential order effect within this cohort. The investigator identified participants who required home assessments based on their VFSS appointment times alone. These appointments were allocated by blinded hospital radiology administrators who were not involved in this study which therefore reduced detection bias.

7.7.6 Magnetic Resonance Imaging (MRI)

MRI studies were completed on one participant with HD pre- and post-treatment. These assessments were part of a concurrent pilot study collecting data regarding cortical changes of patients of various aetiologies under the same protocol. The participant with HD was selected by the timing and location of their participation in the treatment. MRI with diffusion tensor imaging (DTI) utilised standard diffusion protocol with volumetric structural scans and lasted for 30 minutes. All scans were completed at Pacific Radiology at St George's Hospital using a

Siemens MAGNETOM Skyra Maximize 3T scanner (Siemens Healthcare GmbH©). Scans were scheduled on Saturdays two weeks apart, immediately pre- and post- the ten treatment sessions.

Twenty-one white matter tracts were identified as regions of interest. These regions detailed in Table 7.2 and Figure 7.14, were evaluated using two measures: fractional anisotropy (FA), a quantitative measure of the variation of diffusion water in the cortical regions, and mean diffusivity (MD) which provided an indication of the extent of this water diffusion.

Table 7.2

Regions of Interest for DTI analysis

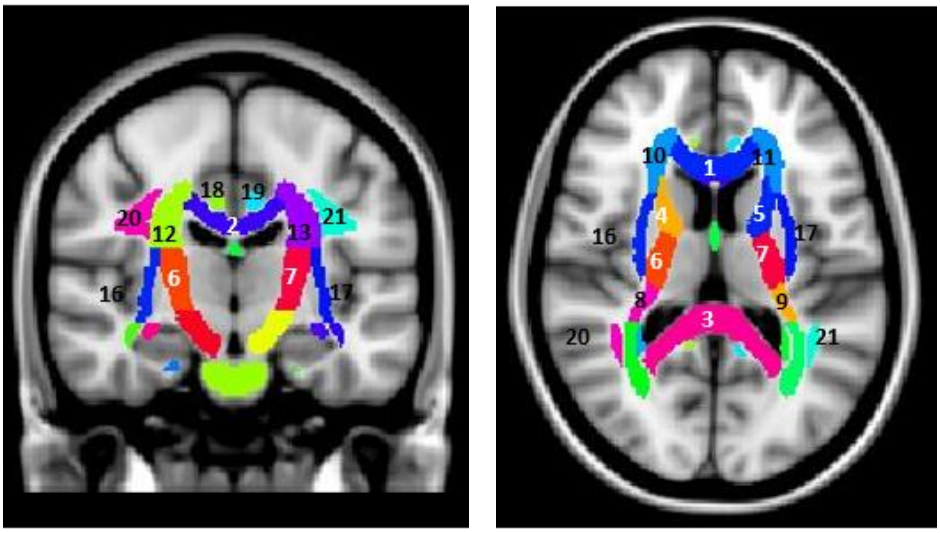
Corresponding Number	White Matter Region
1	Genu of corpus callosum
2	Body of corpus callosum
3	Splenium of corpus callosum
4	Anterior limb of the internal capsule (Right)
5	Anterior limb of the internal capsule (Left)
6	Posterior limb of the internal capsule (Right)
7	Posterior limb of the internal capsule (Left)
8	Retrolenticular part of internal capsule (Right)
9	Retrolenticular part of internal capsule (Left)
10	Anterior corona radiata (Right)
11	Anterior corona radiata (Left)
12	Superior corona radiata (Right)
13	Superior corona radiata (Left)
14	Posterior corona radiata (Right)
15	Posterior corona radiata (Left)
16	External capsule (Right)
17	External capsule (Left)
18	Cingulum (Right)
19	Cingulum (Left)
20	Superior Longitudinal Fasciculus (Right)
21	Superior Longitudinal Fasciculus (Left)

Diffusion-weighted images were pre-processed then statistically analysed by Dr Nadia Borlese according to the following specified methods: “Image pre-processing and statistical analyses were performed using tract-based spatial statistics (TBSS) in FSL 5.0.11 (FMRIB, Oxford, UK), run within Matlab (R2014a) environment (The MathWorks Inc., Natick, Massachusetts, United States). Diffusion-weighted images were motion- and eddy current distortion–corrected. The diffusion tensor was then calculated at each voxel using DTIFIT, producing FA MD images. All FA images were aligned to every other one to identify the “most representative” target subject image. This image was then affine-aligned into MNI152 standard space, and every image transformed into 1x1x1mm MNI152 space by combining the nonlinear transform to the target FA image with the affine transform from that target to MNI152 space. All MD images were transformed into MNI152 standardized space as well.”

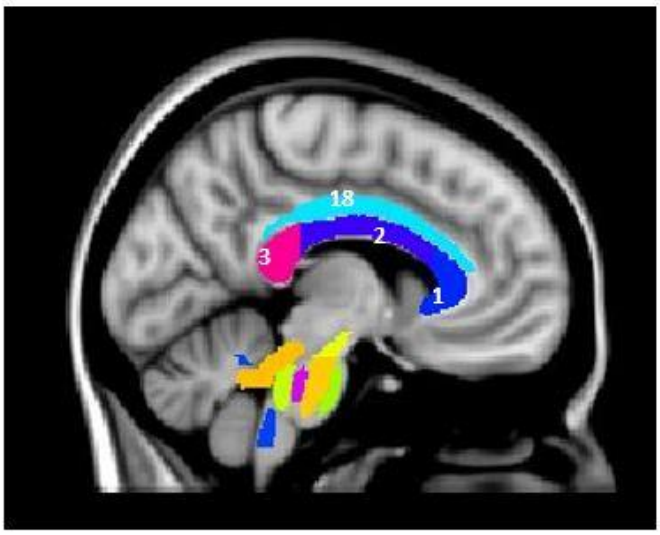
Figure 7.14

White Matter Template of 21 Regions of Interest

(a) (b)



(c)



Note. The corresponding list of regions as detailed Table 7.2. Regions identified in the coronal plane (a), horizontal plane (b) and sagittal plane (c). Images provided by Pacific Radiology Group (Christchurch) DTI report.

7.8 Rehabilitation Protocol

Participants received intervention at a specialised university swallowing laboratory or in their own homes. The treatment protocol within sessions was kept consistent across all participants. The rehabilitative intervention protocol consisted of ten sessions of one-hour daily treatment (five days per week) over two weeks. Ideally, these sessions were scheduled Monday to Friday during both weeks, leaving a two-day break over the weekend. However, if participants were not able to fulfil this optimal schedule, the treatment days were adapted to include weekends to ensure all participants completed ten sessions during the two weeks between pre-treatment and post-treatment assessment sessions.

Treatment utilised sEMG hardware and the custom designed Biofeedback in Strength and Skill Training (BiSSkiT) software as detailed in 'Materials and Instrumentation' (Section 7.6.2). Participants were seated comfortably facing the computer or laptop screen. Investigators ensured that the participant was comfortable to sit for an hour (for instance, had recently been to the toilet) and had a full glass of water or preferred drink within reach. Male participants were asked to be clean shaven for all sessions to ensure adequate sEMG to skin contact. The investigator cleaned the area under the chin with an alcohol wipe and waited at least 20 s for the skin to dry. sEMG electrodes on a small self-adhesive patch were firmly adhered under the participant's chin over the submental muscles (geniohyoid, mylohyoid and anterior belly of the digastric muscles) as depicted in Figure 7.15. The two active electrodes were placed in an anterior to posterior alignment centrally between the spine of the mandible and the superior edge of the thyroid as identified through palpation. The ground electrode was placed laterally over the mandible. The sEMG signal derived from this placement represents collective activation of the floor of mouth muscles during swallowing. The patch and electrodes were also secured with medical tape to keep the patch stable with adequate skin contact. The sEMG

electrodes were attached to a Verity Medical Myotrac Simplex Plus device. For those participants with significant involuntary limb movements, the device was placed behind the participant to minimise interference from accidental contact with the sEMG cables. The sEMG signal was monitored throughout the session by the investigator; electrical interference from the environment such as WIFI modems, laptop chargers and electrical wheelchair chargers were switched off during the session. sEMG resting measurement of < 10 μV was considered optimal and a measurement of > 10 μV required troubleshooting before the session began.

Figure 7.15

Example of Optimal SEMG Electrode Placement for Intervention

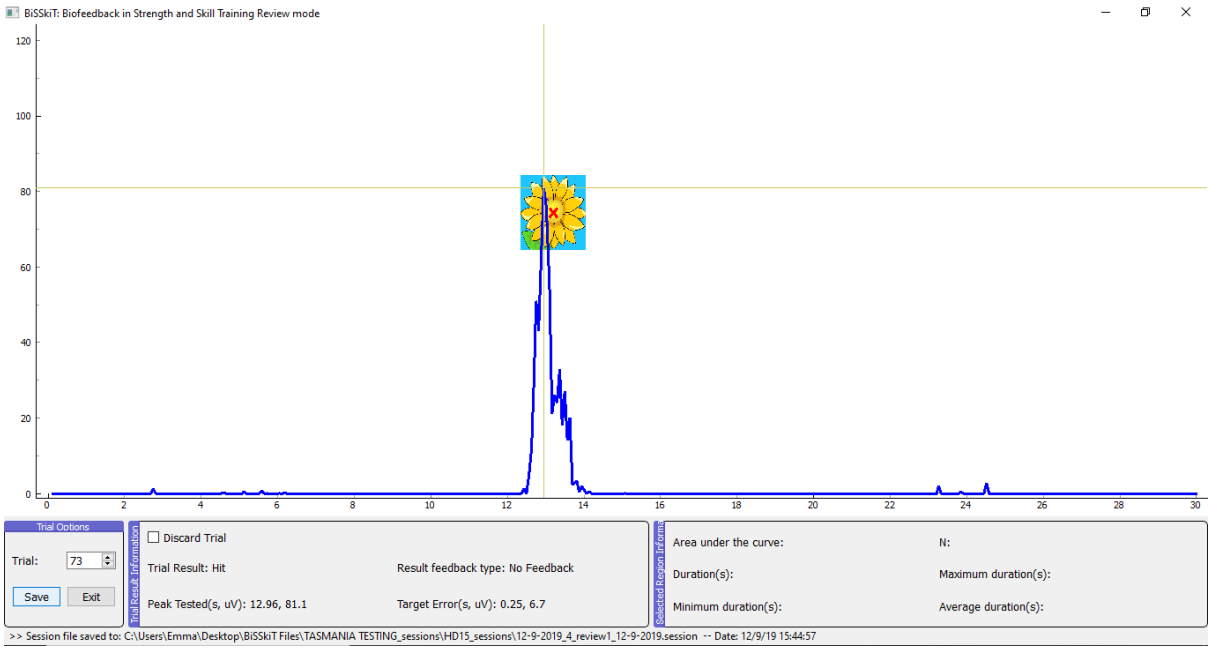
The sEMG signal was transferred via Bluetooth to the BiSSkiT software installed on the laptop or desktop computer. The software was designed to incorporate skill training approaches to improve participants' conscious control and precision over swallowing. Visual feedback is provided as a time by amplitude waveform representing the movement or contraction of the submental muscles. An explanation was given to the participant that peak waveforms could appear during any movements of the jaw or submental muscles, but our focus was on

swallowing events. During the first session, the display of the sEMG signal was set using a calibration sequence, firstly any artefact that elevated the sEMG baseline from zero was corrected by removing DC offset. The participant then completed five effortful swallows over 150 s. Participants were instructed to complete an "effortful swallow" during each 30 second screen. If the investigator judged that the participants were struggling to complete this task, additional instructions such as "imagine you are swallowing a big pill" or "like you are swallowing a big piece of toast" were given and visually modelled. Each calibration swallow representing an "effortful swallow" was identified and marked by right-clicking on the peak of the corresponding waveform. The BiSSkiT software sets the maximal amplitude on the vertical axis as 100% of the averaged five calibration trials. The 'target' box is randomly placed on the screen, between 30% and 70% of the participants' average maximal amplitude during the five effortful swallows. If, after beginning the treatment, the investigator judged that the calibration did not reliably reflect the participant's effortful swallowing magnitude, then re-calibration was completed. This was indicated in cases where the amplitude of the sEMG waveform consistently over-shot the screen range during normal swallowing trials. Calibration values were stored with the file; therefore, re-calibration was not stipulated for each session.

Following calibration, the treatment task commenced. Each 30 second trial required the participant to dry swallow such that the peak of the waveform fell within the centre of the target. Figure 7.16 provides an example of a swallowing trial.

Figure 7.16

Screenshot of a Swallowing Event Hitting the Target Box During one 30 Second Trial

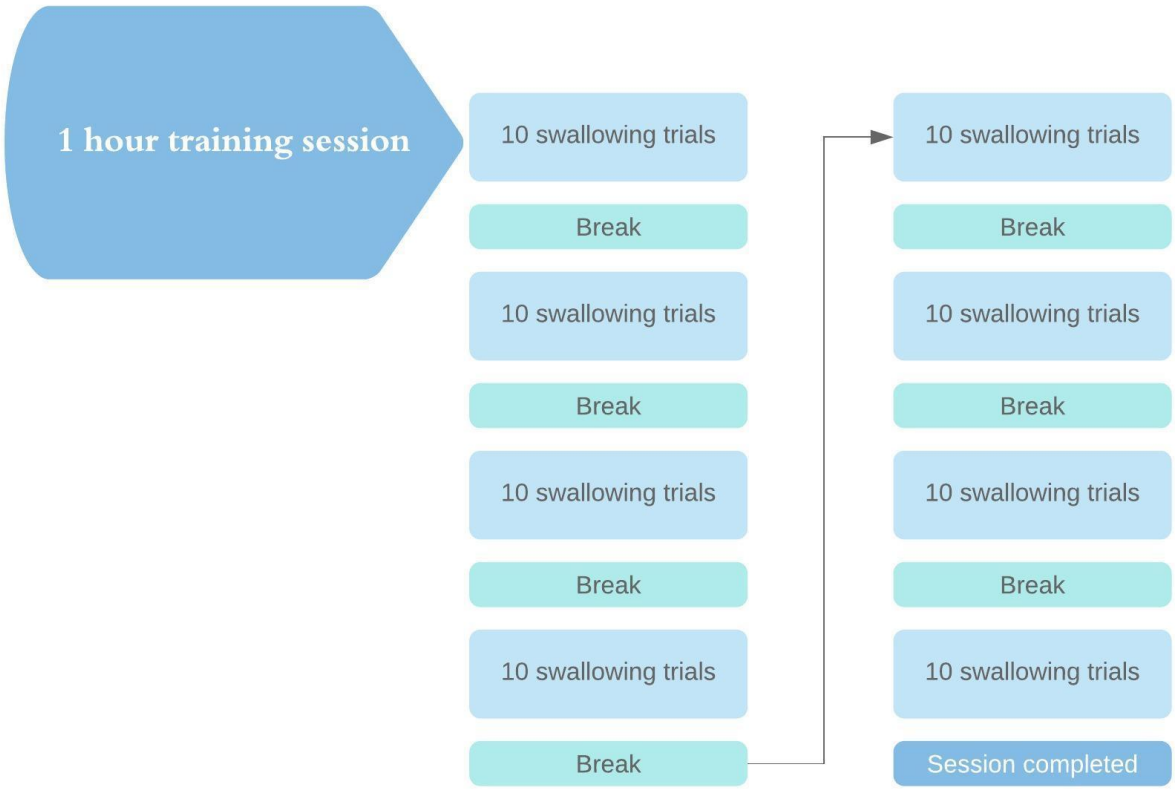


The accuracy and precision of the participant's swallowing skill was targeted as the participant was required to consciously modify the timing and amplitude of their swallowing during each trial, based on feedback from a previous trial. The investigator sat to the side of the participant to observe laryngeal movement and identify each swallowing event by right-clicking the mouse on the corresponding peaked waveform. Participants received immediate visual feedback to inform them of the success of their performance. The task was made more difficult as the participant's accuracy improved the target box decreased by 10% following three consecutive successful 'hits'. The box also increased in size by 10% following three consecutive 'misses' to reduce task difficulty. This adaptation of the BiSSkiT software to increase the challenge of the task with intensity of training, aimed to develop the participants' conscious control of swallowing amplitude and timing. The session 'hit' rate was displayed as a percentage summary of each session. The investigator reviewed all trials after each session to ensure accurate marking of the targeted swallowing event.

Participants completed 80 swallowing trials per session. The number of repetitions was based on the principles of motor learning (Zimmerman et al., 2020), and in line with concurrent treatment studies within the same research laboratory. There were 10 trials per block, and eight blocks per session, as represented in Figure 7.17. Each block of ten trials was separated by a 100 second rest period, during this break, participants were encouraged to take sips of water.

Figure 7.17

Summary of the Format of one Skill-based Training Session Consisting of 80 Swallowing Trails



On completion of the 10 treatment sessions, the investigator exported session summaries from BiSSkiT software to an Excel worksheet. These data were not were not statistically scrutinised

as task performance was not a primary outcome in this research, instead, objective measures of swallowing biomechanics were used to evaluate effectiveness of this intervention. For single case study descriptive analysis, three measurements of task performance were discussed as an indication of skill acquisition; these included: amplitude error (μV from the centre of the target), timing error (seconds from the centre of the target) and total error (mm from the centre of the target).

7.9 Data Storage and Extraction

All raw assessment and treatment data were stored under a unique identifying research number on a password protected hard drive at the Rose Centre for Stroke Recovery and Research at St. George's Medical Centre or a password protected Waitematā District Health Board USB flash drive. The raw research data and subsequent extracted data were kept in a locked cabinet at the Rose Centre. As per University of Canterbury regulations, the data and materials will be deleted after ten years.

Patient demographics for both studies were extracted and analysed descriptively. For the reliability study, the TWST, TOMASS and US data were extracted online. The manofluoroscopic data were coded and extracted offline. For the treatment study, SWAL-QoL data were extracted into Microsoft Excel with pre-set formulae to obtain scores for each of the four parameters (McHorney et al., 2002). The remaining assessment data files were organised by unique participant identifiers. Each data file for TWST, TOMASS, US, VFSS and LRM were assigned a random number by a third researcher who was not involved in this research study to ensure the investigator was blinded to participant and timing of assessment. In contrast to the reliability study, all data were extracted offline for the treatment study by the same raters. After all data had been extracted, the investigator unblinded the data files and set up the .csv

files for analysis in R. Both studies saved de-identified video recordings for all swallowing assessments for subsequent intra-rater and inter-rater reliability analysis.

7.10 Data Analysis

Data were de-identified and analysed using RStudio (version 1.1.453) statistical analysis software and the lme4 package (Bates et al., 2015a).

7.10.1 Intra- and Inter-rater Reliability Analysis

For both studies, intra-rater and inter-rater reliability was calculated using a random 20% of sessions for each outcome measure rated by two blinded raters. Due to the sample being selected at random, each observation was considered independent from each other and was given an observation number. Two independent raters individually measured the selected observations of the TWST, TOMASS, VFSS and US. One rater measured the data twice to obtain two ratings for intra-rater measures a minimum of two weeks apart. The second rater was a trained Speech and Language Therapist (SLT) and researcher with more than four years' experience in dysphagia assessment and diagnosis. Both raters independently extracted data and completed measurements in the research laboratory using software and techniques previously described. Measurements extracted online by the researcher during the test-retest study assessment sessions were then analysed offline for intra-rater analysis.

In both studies, LRM inter-rater measurements were completed by another rater. Due to timing and availability of additional raters, the two studies used different raters. Both raters were experienced SLTs, completing their manometric competencies with three to six months of training, which included interpretation and extraction of data with the specific equipment used in this study. Another researcher completed inter-rater measurements of US data for the

treatment study. This person was a trained SLT and researcher with several years of experience in US measurement of swallowing and developed the guidebook to explicitly describe how to make these specific measurements. All raters underwent informal training, practical measurement sessions and were familiar with the measures prior to data collection. This training took place in combination with another methodological study in the same research setting using US and VFSS procedures. Any questions were discussed with the laboratory supervisors in group meetings using other examples until consensus and learning objectives were reached.

Presence of a potential systematic rater or rating effect was tested by comparing the full model containing 'rater' or 'rating' as a fixed factor to the simplified model excluding them. A *p*-value ≤ .05 was considered significant. One ICC was calculated for both intra- and inter-rater reliability, regardless of multiple bolus types. Therefore, bolus was included in the model as a fixed effect in order to account for variability in the measures with more than one bolus. Intra-rater and inter-rater reliability were calculated using intraclass correlation coefficients ICC (3,1) and ICC (2,1) respectively derived from linear mixed effects models analysis. The model for intra-rater reliability included rating and bolus as a fixed effect and observation number as a random intercept, calculated as:

$$ICC\ (3,1) = \frac{\text{between observation variance}}{\text{between observation variance} + \text{residual variance}}$$

For inter-rater reliability, rater and observation number were included in the model as random intercepts and bolus was included in the model as fixed effect. Inter-rater reliability was then calculated as:

$$ICC\ (2,1) = \frac{\text{between rater variance}}{\text{between rater variance} + \text{between observation variance} + \text{residual variance}}$$

A bootstrap distribution was calculated similar to the test-retest reliability ICC above. The residuals and random effects for each model were tested for normality and heteroskedasticity.

Intra-rater and inter-rater reliability of PAS scores were assessed using the Cohen's Kappa coefficient (*K*) analysis. This analysis was considered superior to overall percent agreement as it incorporates the expected frequency of agreements that could occur by chance (Munoz & Bangdiwala, 1997). A Kappa 0.0 – 0.20 had no agreement, 0.21 – 0.39 was considered 'minimal', 0.4 – 0.59 was 'weak', 0.6 – 0.79 was 'moderate', 0.80 – 0.90 was 'strong' and > 0.90 was considered 'almost perfect' agreement (McHugh, 2012). Kappa was calculated using this formula:

$$K = \frac{\sum \mathrm{a} - \sum \mathrm{ef}}{\mathrm{N} - \sum \mathrm{ef}}$$

The results of the test-retest reliability study aimed to inform the most appropriate and reliable outcome measures to include in the treatment study. This allowed identification of any changes attributable to treatment effect or a decline in function related to the progressive disease process. Table 6.1 (Chapter 6, p. 119) provides a summary of proposed outcome measures.

7.10.2 Test-retest Reliability Statistical Analysis

Test-retest reliability was evaluated for each outcome measure using Type 3 intraclass correlation coefficient ICC (3,1) derived from linear mixed effects models analysis. The model included 'session' as a fixed effect and 'participant' as a random intercept. In order to have one ICC per measure, for each measure including more than one bolus type, the variability of the measure due to bolus was taken into account by including 'bolus' in the model as a fixed effect. The ICC was calculated as:

$$ICC\ (3,1) = \frac{\text{between participant variance}}{\text{between participant variance} + \text{residual variance}}$$

A bootstrap distribution was calculated from which the 95% confidence intervals for each ICC were obtained. ICC values of < 0.5 indicated 'poor', 0.5 – 0.75 indicated 'moderate', 0.75 – 0.9 indicated 'good' and > 0.9 indicated 'excellent' agreement (Koo, 2016). The residuals and random effects for each model were also tested for normality and heteroskedasticity. The standard deviation (SD) of between participants (participant's random intercept SD) and within participant variance (residual SD) were extracted from the model and reported.

7.10.3 Estimated Change Across Sessions Analysis

Mixed effects models were used to calculate estimated change of each measure across assessment sessions. 'Session' was introduced in the model as a fixed effect and participant intercept as a random effect. The estimated percentage of change was calculated from the output of the model as follows:

$$\left(\frac{\text{estimated difference between session A and B}}{\text{estimated mean for session A}}\right) \times 100$$

$$\left(\frac{\text{estimated difference between session A and C}}{\text{estimated mean for session A}}\right) \times 100$$

$$\left(\frac{\text{estimated difference between session B and C}}{\text{estimated mean for session B}}\right) \times 100$$

The estimated percentage of change was utilized for clinical interpretation and to allow for comparison across measures with different units and different numerical meanings. The range for each measure is defined in parenthesis, from the smallest change to largest change based on 95% confidence intervals across sessions. For interpretation of results summarised in Table 8.4 (p.185), the direction of percent change could have been positive or negative across sessions. The residuals and random effects for each model were tested for normality and heteroskedasticity.

7.10.4 Treatment Study: Analysis of Treatment Session Effect

Means and standard deviation (SD) of all outcome measures were calculated across all participants and plotted using scatter plots. Firstly, a likelihood ratio test was conducted using linear mixed effects models analysis. Presence of a session effect was tested by comparing the full models containing 'session' as a fixed factor to the simplified model excluding 'session'. As this is exploratory research, the threshold of $p \leq .07$ was used to select which analyses should be continued using the full model. The selection of a more lenient *p*-value for the initial likelihood ratio interpretation prior to data analysis was justified in this study by the small sample size with larger standard errors and multiple comparisons which reduced the risk of Type I error (Noymer, 2008). If the session effect was $p \leq .07$, analysis using the full model was continued. If there was no session effect, the reduced model was used. A chi-square *p*-

value ≤ .05 was considered significant for interpretation of the full model. Corrections for multiple comparisons were not required as all hypothesis driven comparisons were selected *a priori* (Baguley, 2012). The residuals and random effects for each model were tested for normality and visually inspected to identify any heteroskedastic patterns. If the assumptions of normality were not met, non-parametric Friedman's rank sum test of differences were performed (Hollander, Wolfe & Chicken 2013). Again, a chi-square value *p*-value ≤ .05 was considered significant and a *p*-value of ≤ .07 was discussed. If there was a significant session effect, further pairwise analysis using the Wilcoxon Test was completed.

7.10.5 Rate of Change Analysis

Data for each outcome measure were set up to calculate the rate of change prior to analysis. Data were sorted by participant and bolus to subtract corresponding data from each session. This subset of data were extracted using subtracted data frames and compared. The subtracted sessions were identified *a priori*:

Treatment rate of change – Baseline rate of change:

$$(Assessment\ 3 - Assessment\ 2) - (Assessment\ 2 - Assessment\ 1)$$

Maintenance rate of change – Baseline rate of change:

$$(Assessment\ 4 - Assessment\ 3) - (Assessment\ 2 - Assessment\ 1)$$

Maintenance rate of change - Treatment rate of change:

$$(Assessment\ 4 - Assessment\ 3) - (Assessment\ 3 - Assessment\ 2)$$

Means and SD of all subtracted data were calculated across all participants and plotted using scatter plots. Again, mixed models were utilised to evaluate any difference in the rate of change observed between baseline, treatment and maintenance periods. The full model containing 'session' as a fixed factor was compared to the simplified model excluding 'session'. A chi-square *p*-value ≤ .05 was considered significant. As above, discussion occurred at $p \leq .07$ to

allow for identification of treatment effect close to significant. If the session effect was $p \leq .07$, analysis using the full model was continued. If there was no session effect, the reduced model was used. Again, *p*-value corrections were not required as the comparisons were selected as *a priori* tests of specific hypotheses prior to analysis (Baguley, 2012). The residuals and random effects for each model were tested for normality and visually inspected to identify any heteroskedastic patterns. If assumptions were violated, the same non-parametric analyses were applied as described in 'analysis of treatment effect' above.

7.10.6 Variability of Performance Analysis

As the reliability study identified high variance in participant performance within sessions, the within session variability was compared between assessment sessions. The SD of each assessment which included multiple trials per session were compared. This analysis used SD of outcome measures as the dependent variable to evaluate any session effect on within participant variability. As in the initial analysis of session effect (described in Section 7.10.3), mixed models were compared with and without 'session' as a fixed effect to identify any session effect. A chi-square *p*-value $\leq .05$ was considered significant and a *p*-value of $\leq .07$ was discussed as previously stipulated in this exploratory research. If there was a significant session effect, analysis using the full model was completed. If there was no session effect, the reduced model was used. The normality and homoskedasticity of residuals and random effects were checked, and identical non-parametric analysis methods were used as described in 'analysis of treatment effect' above.

7.10.7 Descriptive Analyses

As this was exploratory work to evaluate the feasibility and effectiveness of this novel skill-based dysphagia training, a single case study was analysed descriptively. This participant was

selected as they completed MRI pre- and post- intervention. Whilst the statistical group analysis was the basis of the results, this additional descriptive case provided individual results in conjunction with MRI data to identify any patient characteristics which may inform future research into the effectiveness of this intervention. This approach addressed the limitations of group-level analysis with this heterogeneous population to accurately observe the effect of treatment for that individual (Harrington & Velicer, 2015).

7.10.8 Penetration-Aspiration Scale Analysis

Descriptive statistics including frequency analysis were used to evaluate PAS scores across assessment sessions. As these ordinal data cannot be considered as interval or continuous (Steele & Grace-Martin, 2017), statistical analysis was not appropriate for this outcome measure. PAS scores across all trials were included in analysis. The use of frequency distributions were recommended by Steele and Grace-Martin (2017) as an appropriate method to accurately represent the categorical data. Alternative methods such as summing PAS scores across the fixed trials, selecting the worst score of the three trials or summarising the mean and median PAS scores all have disadvantages; these methods may not provide a true representation of the patient's airway protection and could increase bias towards impairment during repeated measures.

Chapter 8: Results of Patient Studies

8.1 Test-Retest Study Results

8.1.1 Patient Demographics

Ten participants were identified and recruited via the regional HD Service Coordinator to take part in the test retest reliability study. Nine participants completed all three assessment sessions which included six male and three female participants with a mean age of 44.6 (SD = 12.14). Participant 9 was unable to attend all three sessions as stipulated in the protocol due to transportation issues; their data were not included in the analysis. Participant demographics are summarized in Table 8.1. The number of years since manifestation of symptoms ranged from 2 – 13 years (mean 8.6 years). EAT-10 scores ranged from 4 – 33 ($\bar{x}$ = 11.9). An EAT-10 score of ≥ 3 out of 40 indicates swallowing impairment (Belafsky et al., 2008). Cognitive screening scores derived from the MoCA ranged from 17 – 27 ($\bar{x}$ = 21.6). A MoCA score of ≥ 26 out of 30 indicates normal cognition (Nasreddine et al., 2005). Overall classification of the disease stage of participants was judged using the Shoulson-Fahn Staging Scale in consultation with HD Service Coordinator and ranged from early (Stage II) – late stage (Stage IV) (Shoulson & Fahn, 1979).

Table 8.1

Summary of Participant Demographics for the Test-retest Study

Participant	Gender	Age	Years since onset of symptoms	Shoulson-Fahn Stage	EAT-10 score	Montreal Cognitive Assessment
1	M	41	10	III	13	22
2	F	43	13	IV	18	17
3	M	37	11	III	7	18
4	F	30	9	II	5	27*
5	M	57	5	III	11	22
6	M	32	2	II	7	20
7	M	68	10	III	14	24
8	F	43	9	IV	7	22
9	F	52	13	IV	33	22
10	M	50	4	II	4	25

Note. Participant 9 was excluded from analysis as she did not complete all assessment sessions. *Denotes scores within the range of normal.

8.1.2 Test-Retest Study Inter-rater and Intra-rater Reliability

ICC (3,1) and (2,1) results are summarized in Table 8.2. The TWST and TOMASS measures showed good to excellent inter-rater and intra-rater reliability in 13 of the 14 measures. Eleven of these were > 0.9. US inter-rater reliability was moderate to good (> 0.5 to < 0.9) across 6 out of 7 measures.

Table 8.2

Summary of Inter-rater and Intra-rater Reliability for all Outcome Measures

Assessment	Outcome Measure	Intra-Rater Reliability ICC (3,1)	Inter-Rater Reliability ICC (2,1)
Timed Water Swallow Test	Swallowing capacity (ml per second)	0.99 (0.94, 1.0)	1.0 (0.99, 1.0)
	Swallowing volume (ml per swallow)	0.98 (0.83, 1.0)	0.99 (0.94, 1.0)
	Swallowing time (s per swallow)	0.76 (0.11, 0.97)	0.90 (0.39, 0.98)
Timed Test of Masticating and Swallowing Solids	Number of bites	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
	Number of swallows	1.0 (1.0, 1.0)	0.68 (0.0, 0.95)
	Number of chews	0.95 (0.72, 0.99)	0.77 (0.12, 0.96)
	Time taken (s)	1.0 (0.99, 1.0)	0.94 (0.65, 0.99)
Ultrasound	Hyoid rest (mm)	0.88 (0.56, 1.0) [R]	0.84 (0.74, 0.91) [R]
	Hyoid maximum (mm)	0.48 (0.14, 1.0) [R]	0.46 (0.23, 0.69) [R]
	Percentage change (%)	0.91 (0.64, 1.0) [R]	0.60 (0.41, 0.75) [R]
	Area of geniohyoid [+] (mm^2)	0.77 (0.20, 0.97)	0.62 (0.07, 0.95) [R]
	Area of left anterior belly of digastric (mm^2)	0.86 (0.36, 0.98)	0.76 (0.22, 0.98) [R]
	Area of right anterior belly of digastric (mm^2)	0.95 (0.74, 0.99)	0.88, (0.40, 0.98)
Videofluorscopic Swallowing Studies	Oral transit time (s)	1.00 (1.0, 1.0)	0.19 (0.00, 0.50)
	Pharyngeal transit time (s)	0.94 (0. 73, 1.0) [BR]	0.22 (0.00, 0.55) [BR]
	Total transit time (s)	1.0 (0.97, 1.0)	0.44 (0.11, 0.70)
	Timing of supraglottic closure (s)	1.0(0.97, 1.0)	0.23 (0, 0.56)
	Duration of aryepiglottic closure (s)	0.99 (0.96, 1.0) [R]	0.93 (0.86, 0.97) [R]
	UES duration open (s)	1.0 (0.96, 1.0) [B]	0.51 (0.23, 0.73)
	UES distension (mm)	1.0 (0.96, 1.0)	0.73 (0.50, 0.87)
	Pharyngeal constriction ratio (PCR)	1.0 (0.98, 1.0)	0.59 (0.32, 0.79)

	Hyoid excursion (mm)	1.0 (0.97, 1.0) [B]	0.65 (0.48, 0.81) [B]
Low Resolution Manometry	Sensor 1 peak upper pharynx (mmHg)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
	Sensor 2 peak mid pharynx (mmHg)	0.99 (0.93, 1.0)	1.0 (1.0, 1.0)
	Peak to peak time (s)	1.0 (0.97, 1.0)	0.91 (0.87, 0.94)
	UES minimum pressure (mmHg)	1.0 (0.97, 1.0)	1.0 (0.99, 1.0)
	UES open duration (s)	0.99 (0.95, 1.0)	0.96 (0.93, 0.97)

Note. Outcome measures with a bolus effect are indicated with [B] and a rater or rating effect with [R].

Intra-rater reliability of a random 20% sample of US sessions was measured using two methods. First, the selected still images were remeasured as an assessment of measurement reliability. Second, the investigator scrolled through saved video files to reselect the maximum approximation and rest position of the hyoid to measure. The latter method measured the reliability of both image selection and measurement. Interestingly, the ICC was good to excellent (> 0.75) for 5 out of 6 measures using both methods of measurement. As anticipated, remeasurement from preselected still images had higher intra-rater reliability ($\bar{x}$ ICC = 0.87) compared to remeasurement from video files ($\bar{x}$ ICC = 0.80).

VFSS measures of timing had the lowest inter-rater reliability; 4 of the 7 measures had poor reliability (< 0.5). The duration of aryepiglottic closure had excellent intra-rater and inter-rater reliability (> 0.9). VFSS spatial and displacement measures had moderate to good intra-rater and inter-rater reliability (> 0.5 to < 0.9). LRM demonstrated the highest intra-rater and inter-rater reliability with excellent reliability across all measures (> 0.9).

8.1.3 Test-retest Reliability

Intraclass correlation coefficient (ICC 3,1) results are reported for all measures in Table 8.3. SD between and within participants is also reported for replicability of results. Data were checked for normality and heteroskedasticity of residuals to ensure model assumptions for ICC were met. All data met the assumptions except oral transit time which should be interpreted with caution.

Table 8.3

Summary of Test-retest Reliability for Swallowing Outcome Measures

Assessment	Outcome measure	ICC (3,1) 95% CI within pts	SD between / within participants
Timed Water Swallow Test	Swallowing capacity (ml per second)	0.96 (0.87, 0.99)	10.72 / 2.15
	Swallowing volume (ml per swallow)	0.92 (0.76, 0.98)	9.02 / 2.60
	Swallowing time (s per swallow)	0.88 (0.64, 0.96)	1.49 / 0.56
Timed Test of Masticating and Swallowing Solids	Number of bites	0.39 (0.0, 0.76)	0.70 / 0.88
	Number of chews	0.79 (0.42, 0.93)	11.83 / 6.10
	Number of swallows	0.83 (0.49, 0.95)	0.88 / 0.40
	Time taken (s)	0.70 (0.26, 0.90)	20.87 / 13.57
Ultrasound	Hyoid rest (mm)	0.74 (0.44, 0.87)	4.51 / 2.66
	Hyoid maximum (mm)	0.40[B] (0.14, 0.62)	2.1 / 2.66
	Percentage change (%)	0.44 (0.17, 0.64)	5.65 / 6.39
	Area of geniohyoid[+] (mm^2)	0.69 (0.22, 0.90)	55.34 / 37.31
	Area of left anterior belly of digastric (mm^2)	0.91 (0.75, 0.97)	19.53 / 6.07
	Area of right anterior belly of digastric (mm^2)	0.76 (0.42, 0.92)	19.63 / 11.09
Videofluorscopic Swallowing Studies	Oral Transit Time (s)	0.22 [B] (0.03, 0.45)	0.18 / 0.34
	Pharyngeal Transit Time (s)	0.79 (0.00, 0.90)	0.03 / 0.30
	Total Transit Time (s)	0.21 [B] (0.04, 0.43)	0.21 / 0.4
	Timing of supraglottic closure (s)	0.52 (0.22, 0.72)	0.06 / 0.06
	Duration of aryepiglottic closure (s)	0.50 [B] (0.20, 0.71)	0.29 / 0.29
	UES Duration Open (s)	0.16 [B] (0.01, 0.35)	0.03 / 0.09

	UES Distension (mm)	0.68 (0.37, 0.83)	1.71 / 1.18
	Pharyngeal Constriction Ratio	0.13 (0.02, 0.30)	0.00 / 0.05
	Hyoid excursion (mm)	0.40 [BS] (0.13, 0.62)	4.19 / 5.67
Low Resolution Manometry	Sensor 1 peak upper pharynx (mmHg)	0.41 (0.13, 0.63)	45.11 / 54.25
	Sensor 2 peak mid pharynx (mmHg)	0.36 (0.12, 0.57)	45.25 / 59.61
	Peak to peak time (s)	0.32 [BS] (0.09, 0.53)	0.06 / 0.08
	UES minimum pressure (mmHg)	0.27 (0.06, 0.49)	4.08 / 6.71
	UES open duration (s)	0.36 (0.11, 0.58)	0.11 / 0.15

Note. Outcome measures with a bolus effect are indicated with [B] and session effect indicated with [S]. Standard deviation (SD)of between participant variance contributed to ICC model.

Good to excellent reliability (> 0.75) was seen in 5 out of the 7 TWST and TOMASS assessment parameters. Moderate to excellent reliability (0.69 - 0.91) was found in 4 of the 6 US measures. Measurements of hyoid displacement had poor reliability (< 0.50). VFSS measures ranged from poor to moderate reliability (< 0.5 to < 0.75). All manometric measures produced poor test-retest reliability (< 0.5).

Bolus effects on reliability were observed in 5 of the 9 VFSS outcomes, one US and one LRM outcome. The effect of bolus was included in the model and contributed to variability. Session effects were identified in two measures: hyoid excursion measured by VFSS ($p < 0.001$) was -2.9 mm less in Session B and -2.7 mm less in Session C compared to Session A. The second session effect was found in manometric peak to peak latency ($p = 0.002$) as Session B was -0.0067 s less than Session A and Session C was -0.047 s less than Session A.

8.1.4 Estimated Change Across Sessions

Results of estimated percentage of change across sessions for all outcome measures are summarised in Table 8.4. The range of change is included in parenthesis; this represents the minimum percent change to maximum percent change across sessions. The direction of change across sessions can be positive or negative as the change may increase or decrease. Session effects were noted for the TOMASS number of swallows. Two parameters of US measurement also had session effects which significantly increased values of hyoid excursion by + 1.47 mm ($p = 0.04$) from Session A to Session B. In contrast, decreased values were noted for hyoid excursion, UES distension and oral transit time as measured by VFSS where a session effect was noted ($p < 0.05$). Four out of 5 VFSS session effects were seen with liquid bolus. Significant session effects were noted for dry and puree bolus types for 3 out of 5 LRM outcome measures. For dry swallowing trials, the minimum pressure at Sensor 3 significantly increased ($p < 0.05$) across all sessions (3.26 mmHg, 6.01 mmHg, 2.75 mmHg). Highly significant session effects ($p < 0.001$) were noted for both timing measures during dry swallows with decreased duration of UES opening up to 0.14 s from Session A to B.

Table 8.4

Summary of Variability (average percent change across sessions) for Swallowing Outcome Measures

Outcome measure	Bolus	% Change Session A - Session B (Range)	% Change Session A – Session C (Range)	% Change Session B – Session C (Range)
Timed Water Swallow Test				
Swallowing capacity (ml per second)	NA	-6.82% (10.72 to -24.27)	-9.12% (8.33 to -26.66)	-2.57% (16.25 to -21.29)
Swallowing volume (ml per swallow)	NA	-8.33% (4.86 to -21.52)	-7.78% (5.41 to -20.97)	0.6% (-13.79 to 14.99)
Swallowing time (s per swallow)	NA	0% (-19.77 to -19.77)	0.39% (-19.77 to 20.16)	3.54% (-22.51 to 29.58)
Timed Test of Masticating and Swallowing Solids				
Number of bites	NA	-6.61% (17.72 to -30.93)	-3.3% (21.02 to -27.63)	0.39% (-19.77 to 20.16)
Number of chews	NA	0% (-13.68 to -13.68)	-5.41% (8.24 to -19.1)	-5.41% (8.24 to -19.1)
Number of swallows	NA	-24.1% [S] (-10.79 to -37.41)	-15.83% [S] (-2.52 to -29.14)	10.43% (-7.11 to 27.96)
Time taken (s)	NA	-15.1% (1.21 to -31.4)	-14.66% (1.65 to -30.97)	0.51% (-18.69 to 19.72)
Ultrasound				
Hyoid rest (mm)	Dry	1.36% (-1.48 to 4.15)	1.79% (-1.05 to 4.58)	0.43% (-2.37 to 3.2)
	Liquid	-0.83% (1.98 to -3.63)	-1.84% (0.97 to -4.64)	-1.02% (1.81 to -3.85)
	Puree	-0.57% (2.17 to -3.3)	0.26% (-2.49 to 3)	0.81% (-1.94 to 3.59)
Hyoid maximum (mm)	Dry	3.97% [S] (0.3 to 7.61)	1.81% (-1.89 to 5.45)	-2.08% (1.45 to -5.63)
	Liquid	0.27% (-3.52 to 4.06)	-2.72% (1.1 to -6.51)	-2.98% (0.86 to -6.78)
	Puree	-0.71% (2.98 to -4.42)	-1.93% (1.79 to -5.64)	-1.2% (2.54 to -4.97)
Hyoid percentage change (%)	Dry	-10.41% (3.03 to -23.85)	-1.73% (11.72 to -15.17)	9.69% (-5.41 to 24.85)
	Liquid	-5.43% (7.41 to -18.3)	1.09% (-11.78 to 13.97)	6.93% (-6.81 to 20.63)

	Puree	-0.24% (15.08 to -15.65)	6.3% (-9.07 to 21.63)	6.56% (-8.92 to 22.09)
Area of geniohyoid+ (mm^2)	NA	12.05% (-3.06 to 28.03)	1.98% (-13.12 to 17.97)	-8.98% (4.89 to -22.84)
Area of LAB (mm^2)	NA	3.13% (-4.46 to 10.97)	-5.75% (2.08 to -13.34)	-8.61% [S] (-1.15 to -16.09)
Area of RAB (mm^2)	NA	10.55% (-2.47 to 24.1)	5.77% (-7.25 to 19.32)	-4.32% (7.73 to -16.36)
Videofluoroscopic Swallowing Studies				
Oral transit time (s)	Liquid	-12.5% (16.67 to -37.5)	-4.17% (25 to -33.33)	9.52% (-23.81 to 42.86)
	Puree	15% (-40 to 67.5)	12.5% (-42.5 to 70)	0% (48.89 to -51.11)
Pharyngeal transit time (s)	Liquid	-34.33% (-1.49 to -67.16)	-16.42% (16.42 to -49.25)	26.67% (-24.44 to 75.56)
	Puree	1.69% (-11.86 to 15.25)	0% (13.56 to -15.25)	-1.67% (11.67 to -16.67)
Total transit time (s)	Liquid	-18.39% [S] (-2.3 to -34.48)	-4.6% (12.64 to -20.69)	18.31% (-1.41 to 36.62)
	Puree	7.41% (-13.89 to 29.63)	6.48% (-15.74 to 29.63)	-0.86% (19.83 to -21.55)
Timing of supraglottic closure (s)	Liquid	-200% (400 to -900)	0% (600 to -700)	-200% (500 to -800)
	Puree	0% (-200 to 200)	0% (-200 to 200)	0% (-200 to 200)
Duration of aryepiglottic closure (s)	Liquid	-9.28% (9.28 to -26.8)	-20.62% (-2.06 to -39.18)	-12.36% (6.74 to -32.58)
	Puree	0% (-11.54 to 12.82)	3.85% (-8.97 to 15.38)	2.53% (-8.86 to 15.19)
UES duration open (s)	Liquid	-14.29% (2.86 to -28.57)	0% (-14.29 to -14.29)	16.13% (-3.23 to 32.26)
	Puree	7.69% (-2.56 to 17.95)	10.26% (-2.56 to 20.51)	0% (-9.52 to 11.9)
UES distension (mm)	Liquid	-18% [S] (-7.66 to -28.22)	-9.49% (0 to -19.22)	10.24% (-1.04 to 21.22)
	Puree	-9.14% (-0.13 to -18.28)	-6.89% (2.12 to -15.89)	2.62% (-7.14 to 12.24)
Pharyngeal constriction ratio	Liquid	-25% (25 to -50)	50% (0 to 100)	50% (25 to 100)
	Puree	20% (-20 to 80)	20% (-20 to 80)	0% (-33.33 to -33.33)
Hyoid excursion (mm)	Dry	-5.51% (6.03 to -17.16)	-8.29% (3.67 to -20.2)	-2.94% (10.21 to -15.98)
	Liquid	-13.39% [S] (-0.63 to -26.12)	-20.68% [S] (-7.48 to -33.93)	-8.42% (6.36 to -23.28)

	Puree	-14.65% [S] (-4.07 to -25.22)	-9.11% (1.67 to -19.81)	6.48% (-6.05 to 19.11)
		Low Resolution Manometry		
Sensor 1 max peak (mmHg)	Dry	-2.86% (10.03 to -15.75)	9.98% (-2.91 to 22.86)	13.22% (-0.05 to 26.48)
	Liquid	9.53% (-19.66 to 38.72)	37.62% (8.43 to 66.8)	25.65% (-1.01 to 52.29)
	Puree	23.4% (-3.36 to 50.16)	34.78% (8.02 to 61.53)	9.22% (-12.46 to 30.9)
Sensor 2 max peak (mmHg)	Dry	-9.18% (6.38 to -24.74)	-18.97% (-3.41 to -34.53)	-10.78% (6.35 to -27.91)
	Liquid	2.04% (-22.01 to 26.09)	-4.14% (19.91 to -28.19)	-6.05% (17.52 to -29.62)
	Puree	4.49% (19.71 to 28.69)	-4.15% (20.05 to -28.36)	-8.28% (14.89 to -31.44)
Peak to peak timing (s)	Dry	-55.56% [S] (-33.33 to -77.78)	-38.89% [S] (-16.67 to -55.56)	50% (0 to 100)
	Liquid	-22.22% (0 to -50)	-11.11% (11.11 to 38.89)	14.29% (21.43 to 42.86)
	Puree	-15.79% (5.26 to -36.84)	-21.05% [S] (0 to -42.11)	-6.25% (18.75 to -31.25)
UES min (mmHg)	Dry	-20.88% [S] (-4.16 to -37.22)	-38.5% [S] (-22.17 to -54.52)	-22.27% [S] (-2.51 to 42.11)
	Liquid	-23.51% (6.61 to -54.42)	-25.02% (3.45 to -53.56)	-1.97% (36.37 to -39.38)
	Puree	-17.88% (6.67 to -43.08)	-9.82% (13.04 to -32.67)	9.81% (-2.86 to 14.29)
UES open duration (s)	Dry	-16.67% [S] (-9.52 to -23.81)	-11.9% [S] (-4.76 to -19.05)	5.71% (-2.86 to 14.29)
	Liquid	-10.34% (1.15 to -22.99)	-9.2% (2.3 to -20.69)	1.28% (-11.54 to 14.1)
	Puree	-9.88% [S] (0 to -18.52)	-3.7% (4.94 to -12.35)	6.85% (-2.74 to 16.44)

Note. Outcome measures with a session effect are indicated with [S]. Range represents change across sessions based on 95% confidence intervals. LAB: Left anterior belly of the digastric muscles, RAB: right anterior belly of the digastric muscles.

The TWST and TOMASS measures demonstrated relatively low variability across sessions. Measures acquired from the TWST varied up to 9.12%, whilst measures from the TOMASS varied up to 24.1%. US measures had low variability across sessions (0.27% to 12.05%). Hyoid

rest was least variable with puree bolus trials (0.57% to 0.81%). Area of the geniohyoid^{+} muscles at rest was the most variable US measure (8.98% to 12.05%).

Five of the six VFSS timing measures varied up to 34.33%. Pharyngeal transit time was the least variable with puree bolus (0% to 1.69%) and the most variable with liquid bolus (6.42% to 34.33%). The timing of supraglottic closure skewed the data as it varied 200% from Session A to B and B to C, specifically 0.01 s to -0.01 s. This reflects an estimated change of 0.02 s across all three sessions. The greatest variability was observed between Session A and B on 6 out of 12 timing measurements. Spatial and displacement measures varied across sessions from 0% to 50%. Hyoid excursion with dry swallows had the lowest percent change (2.94% to 8.29%) and UES distension had the lowest variability with a puree bolus (2.62% to 9.14%). PCR had the highest variability with liquid bolus types (25% to 50%). For LRM data, peak to peak timing measurements of dry swallows (38.89% to 55.56%), were most variable. Whilst UES opening duration had the lowest variability with liquid bolus (1.28% from Session B to C). The maximum estimated change of peak amplitude (Sensor 1 and Sensor 2 of LRM) was > 12% in 12 out of 18 measures.

8.2 Treatment Study Results

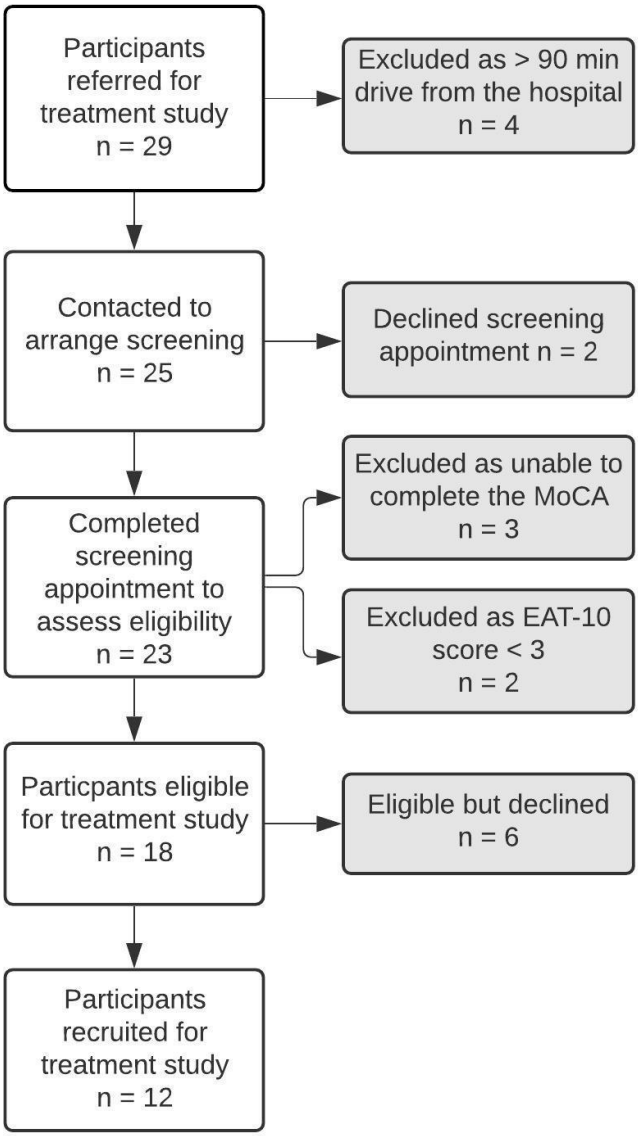
8.2.1 Patient Demographics

The treatment study utilised a convenience sample of consenting participants. As summarised in Figure 8.1, a total of 29 people were referred by health professionals which included 13 referrals in Christchurch and 16 in Auckland. Referrals for people who resided more than 90 minutes from the hospital were excluded as travel for assessments and home visits was not possible. Of note, five of six participants who were eligible but declined to take part in the treatment study had previously completed the test-retest study.

In total, twelve participants completed ten treatment sessions and four assessment sessions as per the study protocol time scales. Eleven participants completed the treatment sessions in their home environment, and one in the University research laboratory private clinic room. For Christchurch participants, the timing, setting, and order of assessments was consistent. In Auckland, all seven participants completed one assessment session with portable assessments in their home environment; four of these sessions were assessment 3 post-therapy and three were assessment 4 maintenance sessions. This was due to hospital radiology appointment allocations, technical problems with the equipment and travel time between appointments. Home-based assessment sessions included TWST, TOMASS, SWAL-QoL and US assessments; the order of assessments and protocols were consistent across different environments excluding VFSS. Four participants completed the SWAL-QoL with staff in their respective care settings. The questionnaire was returned incomplete on two occasions and could not be included in analyses.

Figure 8.1

Flow-chart Diagram to Summarise Participant Recruitment for the Treatment Study



Participant demographics are summarized in Table 8.5. Of the twelve participants, seven were male and five female with a mean age of 51.7 (SD = 15.96). The number of years since manifestation of symptoms ranged from 2 – 27 years ($\bar{x}$ = 10.58 years). Cognitive screening scores ranged from 17 – 27 ($\bar{x}$ = 21.42). EAT-10 scores ranged from 5 – 23 ($\bar{x}$ = 11.92). Overall classification of the disease stage of participants was judged using the Shoulson-Fahn Staging Scale in consultation with HD Service Coordinator, ranging from early (Stage II) – late stage

(Stage IV) (Shoulson & Fahn, 1979). Three participants who lived in care home facilities were on soft diets and five avoided specific textures. All participants completed the TWST and one person chose not to complete the TOMASS due to a lack of dentures.

Table 8.5

Summary of Participant Demographics for the Treatment Study

Participant	Gender	Age	Years since onset of symptoms	Shoulson-Fahn Stage	EAT-10 score	Montreal Cognitive Assessment
1	M	41	10	III	13	22
2	F	43	13	IV	18	17
3	M	37	11	III	7	18
4	F	30	9	II	5	27*
5	F	43	9	IV	7	22
6	M	66	10	IV	18	19
7	M	40	7	II	14	25
8	F	71	27	III	6	21
9	F	41	4	III	9	23
10	M	81	5	III	10	21
11	M	58	2	II	13	21
12	M	63	20	IV	23	21

Note. *Denotes scores within the range of normal.

The optimum treatment schedule was five sessions per week Monday to Friday over two weeks with a two-day break. This was not possible in eight participants and the session was re-arranged to take place one day during the weekend. VFSS appointments in Auckland were

allocated on Fridays only; therefore, the Friday of the second week of treatment was required to be an assessment session. Other reasons that prohibited optimum scheduling included other medical appointments, funeral attendance and investigator illness.

8.2.2 Treatment Study Intra-rater and Inter-rater Reliability

Although rater-reliability was investigated as part of the previous test-retest reliability study, it was necessary to evaluate intra-rater and inter-rater reliability of this specific cohort in order to reliably interpret the treatment study results. ICC (3,1) and (2,1) results based on 95% confidence interval are summarized in Table 8.6. The TWST and TOMASS measures were derived with good to excellent intra-rater and inter-rater reliability in 10 of the 14 measures: six of these were > 0.90. US intra-rater and inter-rater reliability was moderate to good (> 0.5 to < 0.9) across all measures. This analysis included image selection and measurement from each video. Data from inter-rater reliability measurement of the area of submental muscles did not meet model assumptions and should be interpreted with caution.

Table 8.6

Summary of Inter-rater and Intra-rater Reliability for all Outcome Measures

Assessment	Outcome Measure	Intra-rater Reliability ICC (3,1)	Inter-rater Reliability ICC (2,1)
Timed Water Swallow Test	Swallowing capacity (mls per second)	0.99 (0.95, 1.0)	0.98 (0.91, 1.0)
	Swallowing volume (mls per swallow)	0.98 (0.92, 1.0)	0.99 (0.93, 0.99)
	Swallowing time (s per swallow)	0.86 (0.53, 0.96)	0.86 (0.49, 0.96)
Timed Test of Masticating and Swallowing Solids	Number of bites	0.96 (0.89, 1.0)	0.96 (0.57, 1.0)
	Number of chews	0.65 (0.00, 0.98)	0.74 (0.00, 0.98)
	Number of swallows	0.32 (0.00, 0.96)	0.29 (0.0, 0.92)
	Time taken (s)	0.76, (0.20, 0.99)	0.75 (0.00, 0.98)

Ultrasound	Percentage change (%)	0.88 (0.83, 0.92)	0.69 (0.67, 0.79)
	Area of geniohyoid^{+} (mm^2)	0.83 (0.45, 0.95)	0.80 (0.00, 0.99)
	Area of left anterior belly of digastric (mm^2)	0.91 (0.67, 0.98)	0.87 (0.22, 0.99)
	Area of right anterior belly of digastric (mm^2)	0.53 (0.00, 0.86)	0.81 (0.00, 0.99)
Videofluorscopic Swallowing Studies	Oral transit time (s)	0.85 (0.77, 0.91) [BR]	0.77 (0.60, 0.87) [BR]
	Pharyngeal transit time (s)	0.75 (0.63, 0.85)	0.62 (0.46, 0.77)
	Total transit time (s)	0.92 (0.88, 0.96) [BR]	0.89 (0.79, 0.95) [BR]
	Timing of supraglottic closure (s)	0.66 (0.50, 0.79) [BR]	0.34 (0.12, 0.57) [BR]
	Aryepiglottic closure duration (s)	0.85 (0.78, 0.91) [B]	0.29 (0.05, 0.45) [BR]
	UES duration open (s)	0.54 (0.36, 0.70)	0.49 (0.28, 0.67) [R]
	UES distension (mm)	0.61 (0.43, 0.75) [R]	0.47 (0.24, 0.67) [R]
	Pharyngeal constriction ratio	0.76 (0.64, 0.85)	0.65 (0.47, 0.79) [R]
	Hyoid excursion (mm)	0.88 (0.83, 0.93)	0.59 (0.44, 0.72)
Low Resolution Manometry	Sensor 1 peak upper pharynx (mmHg)	1.0 (1.0, 1.0)	1.0 (0.99, 1.0)
	Sensor 2 peak mid pharynx (mmHg)	0.87 (0.80, 0.93)	0.87 (0.79, 0.93)
	Peak to peak time (s)	0.95 (0.92, 0.98)	0.95 (0.91, 0.98)
	UES minimum pressure (mmHg)	1.0 (1.0, 1.0)	1.0 (0.99, 1.0)
	UES open duration (s)	0.99 (0.98, 0.99)	0.94 (0.89, 0.97)

Note. Outcome measures with a bolus effect are indicated with [B] and a rater or rating effect with [R].

Good to excellent intra-rater reliability (> 0.75, > 0.9) was observed in 6 out of 9 VFSS measurements. Of the timing measures, total transit time had the highest intra-rater reliability (ICC = 0.92) and UES duration opening had the lowest intra-rater reliability (ICC = 0.54). Inter-rater reliability of VFSS measurements were lower across all parameters. Five of the 9

measures were extracted with moderate to good reliability (ICC = 0.5 – 0.9). Again, total transit time had the highest reliability (ICC = 0.89). Aryepiglottic closure duration had the lowest inter-rater reliability (ICC = 0.29); however, the data violated the model assumptions and should be interpreted with caution. Low resolution manometry demonstrated the highest intra-rater and inter-rater reliability with excellent reliability across all measures (> 0.9). Intra-rater reliability of Penetration-Aspiration Scale (PAS) ratings was 'strong' k = 0.84 (95% absolute agreement); however inter-rater reliability was 'minimal' k = 0.38 (78% absolute agreement). The most common difference in score was between PAS = 2 and PAS = 4, which the second rater scored higher on 8 out of 13 disagreements.

8.2.3 Session Effect Analysis

The mean and SD of each outcome measure across participants are summarised in Appendix E. Presence of a session effect was tested by comparing models with and without 'session' as a fixed factor. Results of this initial likelihood ratio session effect analysis are presented in Table 8.7. A significant session effect was found in the 'secretion symptoms' parameter of the SWAL-QoL ($p = 0.05$). 'Pharyngeal symptoms' and 'total' parameters were close to statistical significance ($p = 0.07$); therefore, further analyses were completed using the reduced model. Results of the analysis including 'session' as a fixed effect are summarised in Table 8.8. There was a significant treatment effect (between Assessment 2 and 3) with an increase in self-reported QoL scores across all three parameters of the SWAL-QoL ($p < 0.05$).

Table 8.7

Results of Initial Analysis of Session Effect for Parametric Data

Assessment	Outcome Measure	Bolus	Chi-Squared (df)	*p* - value
SWAL - QoL	Oral symptoms	NA	χ^2 (3) = 3.28	0.35
	Pharyngeal symptoms	NA	χ^2 (3) = 6.96	0.07
	Secretion symptoms	NA	χ^2 (3) = 7.89	0.05*
	Total	NA	χ^2 (3) = 7.16	0.07
Timed Test of Masticating and Swallowing Solids	Number of bites	NA	χ^2 (3) = 0.47	0.93
	Number of swallows	NA	χ^2 (3) = 2.96	0.40
	Time taken (s)	NA	χ^2 (3) = 6.91	0.07
Ultrasound	Percentage change (%)	Dry Liquid Puree	χ^2 (3) = 4.60 χ^2 (3) = 4.02 χ^2 (3) = 7.38	0.20 0.26 0.06
	Area of geniohyoid$^+$ (mm^2)	NA	χ^2 (3) = 2.01	0.57
	Area of left anterior belly of digastric (mm^2)	NA	χ^2 (3) = 2.43	0.49
	Area of right anterior belly of digastric (mm^2)	NA	χ^2 (3) = 5.46	0.14
Videofluorscopic Swallowing Studies	Pharyngeal transit time (s)	Liquid	χ^2 (3) = 4.00	0.26
	Total transit time (s)	Liquid Puree	χ^2 (3) = 7.39 χ^2 (3) = 2.34	0.06 0.51
	Timing of supraglottic closure (s)	Liquid Puree	χ^2 (3) = 1.74 χ^2 (3) = 3.80	0.63 0.28
	Duration of aryepiglottic closure (s)	Puree	χ^2 (3) = 5.95	0.11
	UES duration open (s)	Liquid Puree	χ^2 (3) = 3.54 χ^2 (3) = 6.61	0.32 0.09
	UES distension (mm)	Liquid Puree	χ^2 (3) = 5.74 χ^2 (3) = 9.27	0.13 0.03*
	Pharyngeal constriction ratio	Liquid Puree	χ^2 (3) = 3.21 χ^2 (3) = 8.76	0.36 0.03*

	Hyoid excursion (mm)	Dry Liquid Puree	χ^2 (3) = 7.35 χ^2 (3) = 3.87 χ^2 (3) = 3.21	0.06 0.28 0.36
Low Resolution Manometry	Sensor 1 peak upper pharynx (mmHg)	Dry Liquid Puree	χ^2 (3) = 10.74 χ^2 (3) = 8.37 χ^2 (3) = 2.22	0.01* 0.04* 0.53
	Sensor 2 peak mid pharynx (mmHg)	Dry Liquid Puree	χ^2 (3) = 6.76 χ^2 (3) = 4.0 χ^2 (3) = 3.08	0.08 0.26 0.38
	Peak to peak time (s)	Dry Liquid Puree	χ^2 (3) = 5.41 χ^2 (3) = 5.21 χ^2 (3) = 11.14	0.14 0.16 0.01*
	UES minimum pressure (mmHg)	Dry Liquid Puree	χ^2 (3) = 16.50 χ^2 (3) = 1.98 χ^2 (3) = 0.45	< 0.001* 0.58 0.93
	UES open duration (s)	Dry Liquid Puree	χ^2 (3) = 1.51 χ^2 (3) = 8.27 χ^2 (3) = 9.84	0.68 0.04* 0.02*

Table 8.8

Results of the Post-hoc Analysis of Session Effect Including 'Session' as a Fixed Effect

Outcome measure	Bolus	Sessions Compared	Estimated Change	95% CI	*p* - value
SWAL-QoL (Pharyngeal symptoms)	NA	II-I	-1.73	[-10.33, 6.87]	0.61
		III-II	8.12	[-0.77, 17.00]	0.03*
		IV-III	-2.17	[-2.17, 6.72]	0.54
SWAL-QoL (Secretion symptoms)	NA	II-I	-14.09	[-30.06, 1.89]	0.03*
		III-II	13.83	[-2.67, 30.33]	0.04*
		IV-III	0.75	[-15.75, 17.25]	0.91
SWAL-QoL (Total symptoms)	NA	II-I	-1.41	[-9.24, 6.42]	0.65
		III-II	7.66	[-0.43, 15.75]	0.02*
		IV-III	-2.60	[-10.69, 5.50]	0.42
TOMASS (Time)	NA	II-I	6.45	[-9.51, 22.52]	0.31
		III-II	2.63	[-13.33, 18.60]	0.67
		IV-III	-14.93	[-30.89, 1.03]	0.02*
Ultrasound (% Change)	Puree	II-I	-0.95	[-4.59, 2.68]	0.50
		III-II	-2.52	[-6.15, 1.12]	0.08
		IV-III	0.84	[-2.80, 4.47]	0.56
VFSS (Total transit time)	Liquid	II-I	-0.13	[-0.23, -0.001]	0.01*
		III-II	0.09	[-0.03, 0.22]	0.05*
		IV-III	-0.03	[-0.15, 0.08]	0.46
VFSS (UES distension)	Puree	II-I	0.06	[-0.55, 0.66]	0.81
		III-II	-0.58	[-1.18, 0.03]	0.02*
		IV-III	0.64	[0.04, 1.24]	0.007**
VFSS (PCR)	Puree	II-I	0.03	[-0.01, 0.06]	0.05*
		III-II	0.003	[-0.03, 0.04]	0.82
		IV-III	-0.03	[-0.06, 0.00]	0.05*
VFSS (Hyoid Excursion)	Dry	II-I	-3.56	[-7.33, 0.22]	0.02*
		III-II	0.33	[-3.45, 4.10]	0.83
		IV-III	0.41	[-3.42, 4.25]	0.78
LRM (Sensor 1 maximum pressure)	Dry	II-I	18.31	[-6.63, 43.25]	0.06
		III-II	3.48	[-21.46, 28.42]	0.72
		IV-III	-26.29	[-50.89, -1.68]	0.007*
	Liquid	II-I	24.32	[-7.40, 56.05]	0.06
		III-II	-5.55	[-37.28, 26.17]	0.66
		IV-III	-25.37	[-25.37, 6.36]	0.05*
LRM (Peak to peak time)	Puree	II-I	0.04	[-0.03, 0.12]	0.13
		III-II	0.05	[-0.02, 0.12]	0.07
		IV-III	-0.07	[-0.14, 0.00]	0.02*
LRM (Sensor 3 Minimum pressure)	Dry	II-I	-7.41	[-13.09, -1.72]	0.001**
		III-II	1.74	[-3.94, 7.42]	0.43
		IV-III	-2.76	[-8.97, 2.75]	0.21
LRM (UES duration open)	Liquid	II-I	0.11	[-0.07, 0.29]	0.13
		III-II	-0.03	[-0.21, 0.15]	0.65
		IV-III	-0.16	[-0.16, 0.03]	0.03*
	Puree	II-I	0.12	[-0.07, 0.30]	0.11

III-II	-0.10	[-0.29, 0.09]	0.18
IV-III	-0.13	[-0.32, 0.06]	0.09

Note. CIs: confidence intervals

All parameters of the TWST violated model assumptions of normality and homoscedasticity; therefore, non-parametric analyses were completed and summarised in Table 8.9. There were no significant session effects on capacity, volume or time as measured with the TWST ($p > 0.05$). Similarly, none of the TOMASS outcome measures reached significance ($p > 0.05$). However, the TOMASS timing measure was sufficiently close to significant to complete the post-hoc analysis ($p = 0.07$). There was a significant reduction in time taken between post-treatment (Assessment 3) and maintenance (Assessment 4).

All US outcome measures met model assumptions. There were no significant effects of session on initial analysis ($p > 0.05$). Hyoid excursion (percentage change) with puree bolus reduced during treatment; this did not reach statistical significance. Four of out the eight VFSS outcome measures were analysed using the reduced model to evaluate session effects. One out of the six timing measurements had a significant session effect. There was a significant decrease in total transit time with liquids during baseline (between Assessment 1 and 2), and a significant increase in total transit time with liquids during treatment (between Assessments 2 and 3). Displacement measurement of UES distension with puree bolus trials had a significant treatment effect, reducing from 6.95 mm (SD 1.47) to 6.35 mm (SD1.26) between Assessments 2 and 3. In contrast, there was then a significant increase of during the maintenance period (between Assessment 3 and 4). There was a significant session effect of PCR with puree trials only, with an increase during baseline and a decrease during maintenance. Unlike US outcome measurement of hyoid excursion, there was a significant session effect as measured via VFSS:

hyoid excursion during dry swallowing trials decreased during the baseline period (between Assessment 1 and 2).

Four of the five LRM outcome measures showed a significant session effect ($p > 0.05$). Pharyngeal pressure measured at Sensor 1 in the upper pharynx significantly decreased during the maintenance period (between Assessment 3 and 4) during dry and liquid bolus trials. This outcome measure was noted to have the highest variation in data as represented in the largest 95% CIs. In contrast, minimum pressure at Sensor 3 during dry swallowing trials significantly decreased during baseline treatment ($p = 0.001$) but increased during the treatment phase ($p = 0.21$). Both LRM timing measurements had significant session effects: peak to peak latency between Sensor 1 and 2 peak waveforms was significantly shorter with puree trials during the maintenance period. The duration of UES opening was also significantly decreased during the maintenance period; this effect was only found with liquid bolus trials.

Outcome measures summarised in Table 8.9. did not meet the assumptions of normality and homoscedasticity were subsequently analysed with non-parametric Friedman rank sum test. None of these swallowing outcomes had a significant session effect ($p > 0.05$).

Table 8.9

Results of Friedman Rank Sum Tests to Analyse Session Effect for Non-parametric Data

Assessment	Outcome Measure	Medians (Assessments 1, 2, 3, 4)	Friedman Chi-Squared (df)	*p* - value
Timed Water Swallow Test	Swallowing capacity (ml per second)	5.78, 4.63, 3.66, 5.23	2.64 (3)	0.45
	Swallowing volume (ml per swallow)	14.32, 12.18, 12.02, 10.77	6.83 (3)	0.08
	Swallowing time (s per swallow)	2.74, 2.48, 2.44, 2.61	1.32 (3)	0.72
Timed Test of Masticating and Swallowing Solids	Number of masticatory cycles	40, 37, 39, 36	4.95 (3)	0.18
Videofluorscopic Swallowing Studies	Oral transit time (s)	Liquid: 0.2, 0.16, 0.2, 0.16	5.29 (3)	0.15
		Puree: 0.23, 0.34, 0.36, 0.29	0.7 (3)	0.87
	Pharyngeal transit time (s)	Puree: 0.53, 0.52, 0.48, 0.51	2.70 (3)	0.44
	Duration of aryepiglottic closure (s)	Liquid: 0.69, 0.88, 0.72, 0.74	6.4 (3)	0.09

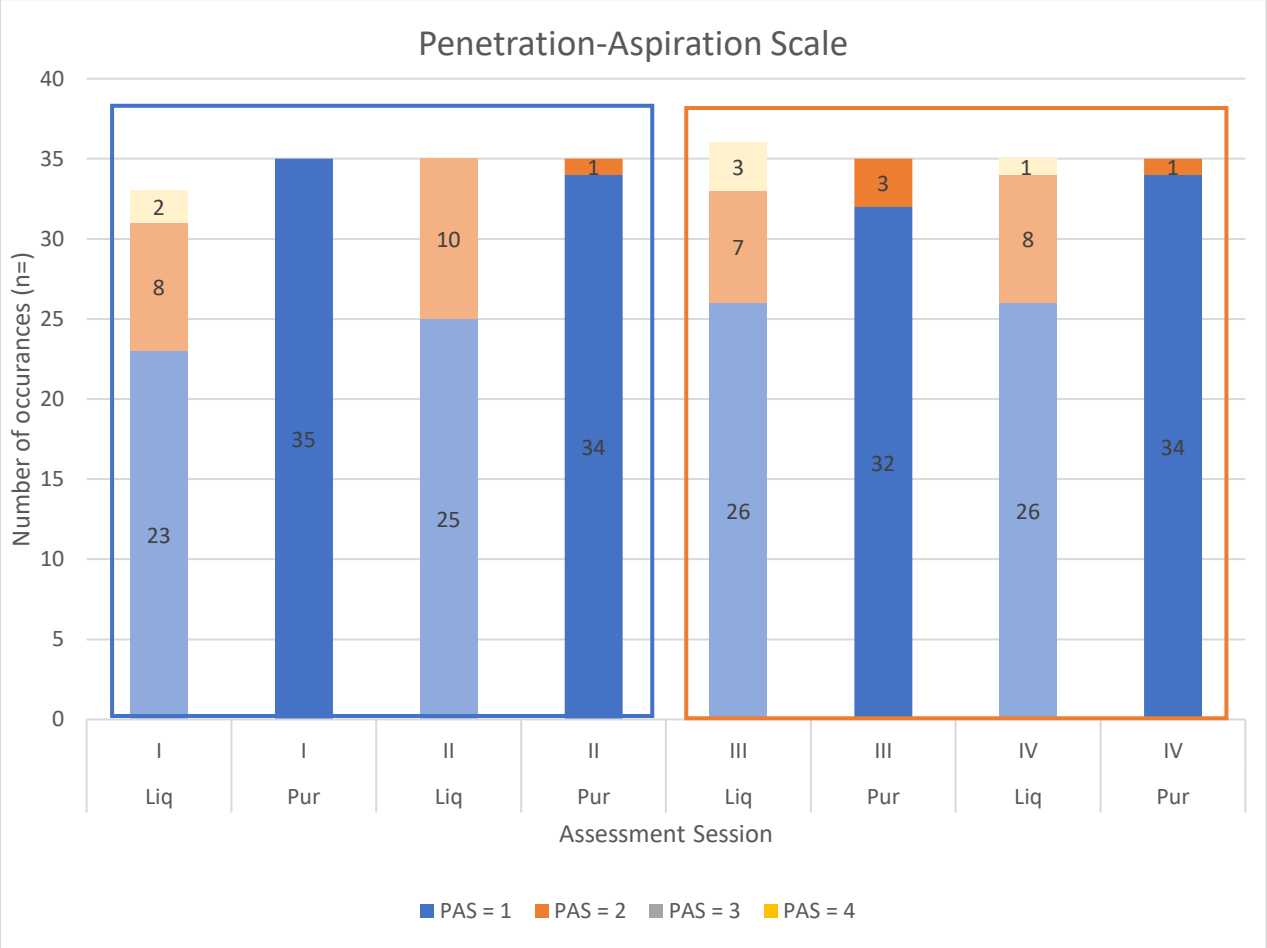
8.2.3.1 Penetration-Aspiration Scale

VFSS videos were sufficiently clear to allow for PAS judgement in 35 out of 36 videos during puree bolus trials for each assessment session. For liquid bolus trials 33 out of 36 trials were scored from Assessment 1, all trials were analysed during Assessment 3, and 35 were scored for both Assessments 2 and 4. From the eight-point scale, only scores of 1, 2 or 4 were recorded in this cohort. Results are summarised in Figure 8.2. PAS 1 was recorded more frequently post-therapy with liquid bolus trials (n = 26). There were fewer occurrences of PAS 2 post-therapy (n = 7) compared to pre-therapy (n = 10). PAS 4 occurred in n = 3 trials in post-therapy compared to n = 2 at baseline. PAS judgement of puree swallowing trials had little variability

across all four assessment sessions as 96% of all trials were judged as PAS 1. The greatest number of PAS 2 occurrences were observed post-therapy (n = 3).

Figure 8.2

Results of Penetration-Aspiration Scale According to Assessment Session and Bolus



Note. Columns within the blue box represent pre-therapy and columns within the orange box represent post-therapy. Liq: Liquid bolus trials, Pur: Puree bolus trials. Pale coloured columns represent liquid bolus data across assessment sessions and strong coloured columns highlight puree bolus data across assessment sessions. Of the 8-point PAS, only scores of 1,2 and 4 occurred.

8.2.4 Rate of Change Analysis

None of the outcome measures in this data analysis met the model assumptions of normality and homoscedasticity. Therefore, non-parametric tests were utilised. Table 8.10 provides the summary of all data calculated using Friedman rank sum tests.

Table 8.10

Summary of Rate of Change Results Completed Using Friedman's Rank Sum Tests

Assessment	**Outcome Measure**	**Bolus**	**Medians (Assessments 2 – 1/ 3 – 2/ 4 – 3)**	**Friedman Chi-Squared (df)**	***p* - value**
SWAL - QoL	Oral symptoms	NA	0.0 / 4.17 / -8.33	3.20 (2)	0.20
	Pharyngeal symptoms	NA	-3.57 / 7.14 / -7.11	4.29 (2)	0.12
	Secretion symptoms	NA	-12.5 / 18.75 / 0.00	7.09 (2)	0.03*
	Total	NA	0.0 / 5.36 / 0.90	0.89 (2)	0.64
TWST	Swallowing capacity (ml per second)	NA	0.0 / -1.01 / 0.0	2.74 (2)	0.25
	Swallowing volume (ml per swallow)	NA	0.16 / -0.45 / 0.17	0.50 (2)	0.78
	Swallowing time (s per swallow)	NA	0.02 / 0.0 / -0.22	0.50 (2)	0.78
TOMASS	Number of bites	NA	0 / 0 / 0	0.42 (2)	0.81
	Number of masticatory cycles	NA	-2 / 2 / -3	3.62 (2)	0.16
	Number of swallows	NA	0 / 0 / 0	2.36 (2)	0.31
	Time taken (s)	NA	1 / 2 / -11	3.45 (2)	0.18
US	Percentage change (%)	Dry Liquid Puree	3.41 / -2.47 / 3.90 -2.37 / - 1.34 / 0.48 -0.45 / -3.40 / 0.97	2.17 (2) 1.17 (2) 1.50 (2)	0.34 0.56 0.47
	Area of geniohyoid^{+} (mm^2)	NA	-19.95 / 22.79 / -7.22	4.67 (2)	0.09

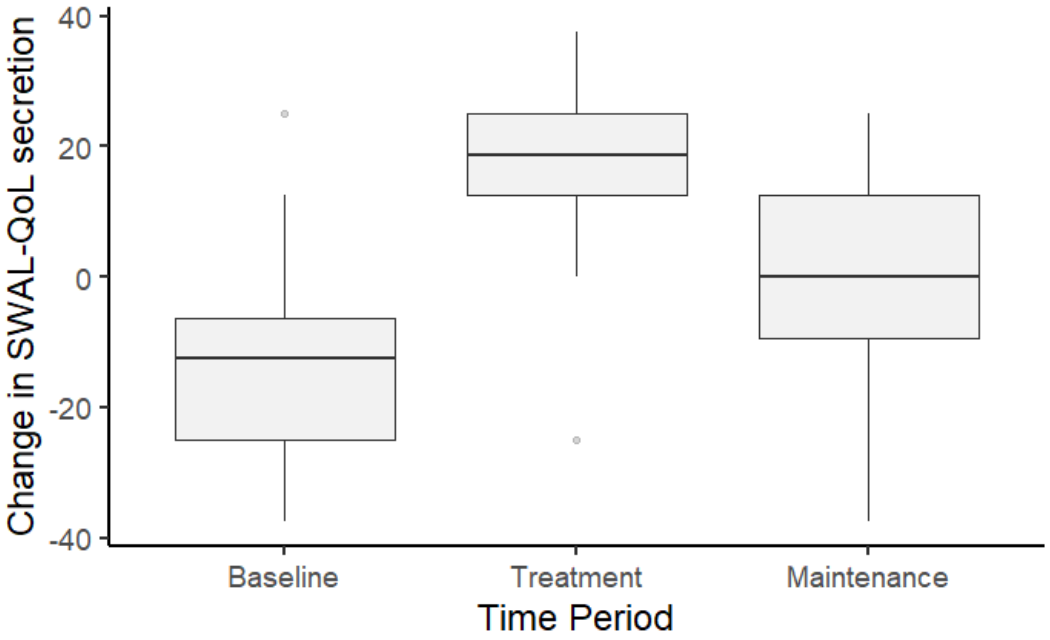
	Area of left anterior belly of digastric (mm^2)	NA	3.22 / 14.13 / -2.19	5.17 (2)	0.08
	Area of right anterior belly of digastric (mm^2)	NA	-14.48 / 8.92 / 4.49	3.17 (2)	0.21
VFSS	Oral transit time (s)	Liquid Puree	-0.12 / 0.06 / -0.02 0.09 / 0.02 / -0.08	10.36 (2) 0.67 (2)	0.006* 0.72
	Pharyngeal transit time (s)	Liquid Puree	0.01 / 0.04 / -0.03 -0.002 / -0.04 / 0.05	2.43 (2) 2.68 (2)	0.30 0.26
	Total transit time (s)	Liquid Puree	-0.05 / 0.07 / -0.05 0.11 / -0.07 / -0.10	8.73 (2) 0.67 (2)	0.01* 0.72
	Timing of supraglottic closure (s)	Liquid Puree	0.01 / 0.02 / -0.00 0.00 / 0.00 / 0.00	0.67 (2) 0.17 (2)	0.72 0.92
	Duration of aryepiglottic closure (s)	Liquid Puree	0.21 / -0.08 / -0.02 -0.03 / 0.02 / -0.02	1.50 (2) 4.50 (2)	0.47 0.11
	UES duration open (s)	Liquid Puree	0.01 / 0.01 / -0.03 -0.02 / -0.03 / 0.04	3.11 (2) 0.17 (2)	0.21 0.92
	UES distension (mm)	Liquid Puree	0.59 / 0.03 / -0.27 0.25 / -0.27 / 0.76	2.40 (2) 1.50 (2)	0.30 0.47
	Pharyngeal constriction ratio	Liquid Puree	-0.01 / 0.03 / -0.00 0.01 / 0.00 / -0.01	0.20 (2) 3.82 (2)	0.90 0.15
	Hyoid excursion (mm)	Dry Liquid Puree	-3.59 / 1.22 / 0.58 -0.66 / 2.74 / 1.30 -1.32 / -0.31 / 2.99	3.50 (2) 2.00 (2) 2.17 (2)	0.17 0.37 0.34
LRM	Sensor 1 peak upper pharynx (mmHg)	Dry Liquid Puree	12.95 / 4.75 / -30.61 0.38 / -2.19 / -29.44 8.55 / -18.28 / 0.72	3.50 (2) 2.00 (2) 0.00 (2)	0.17 0.37 1
	Sensor 2 peak mid pharynx (mmHg)	Dry Liquid Puree	13.63 / -34.13 / 49.54 4.84 / -60.92 / 48.47 45.65 / -22.23 /-20.51	1.50 (2) 0.50 (2) 1.50 (2)	0.47 0.78 0.47
	Peak to peak time (s)	Dry Liquid Puree	0.02 / 0.01 / -0.03 0.02 / 0.05 / -0.06 0.02 / 0.05 / -0.03	3.50 (2) 0.50 (2) 3.50 (2)	0.17 0.78 0.17
	UES minimum pressure (mmHg)	Dry Liquid Puree	-9.94 / 2.46 / -1.01 -0.25 / 0.46 / -1.09 3.55 / 1.05 / 0.88	1.50 (2) 0.00 (2) 1.50 (2)	0.47 1 0.47

	UES open duration (s)	Dry	-0.05 / 0.02 / -0.05	0.00 (2)	1
		Liquid	0.11 / -0.03 / -0.18	0.50 (2)	0.78
		Puree	0.13 / -0.06 / -0.19	0.50 (2)	0.78

There were no significant differences in the rate of change across baseline, treatment and maintenance periods on oral, pharyngeal or total parameters of the SWAL-QoL. The secretion symptoms subsection had a significantly different rate of change across assessment sessions ($p < 0.05$) and was subsequently analysed with Wilcoxon. The increased rate of change between baseline and treatment was significant ($V = 2$, $p = 0.02$*), and between baseline and maintenance change ($V = 41$, $p = 0.03$*). The direction of change in secretion scores is summarised in Figure 8.3.

Figure 8.3

Representation of the Distribution of SWAL-QoL Secretion Score Rate of Change Across Time Periods

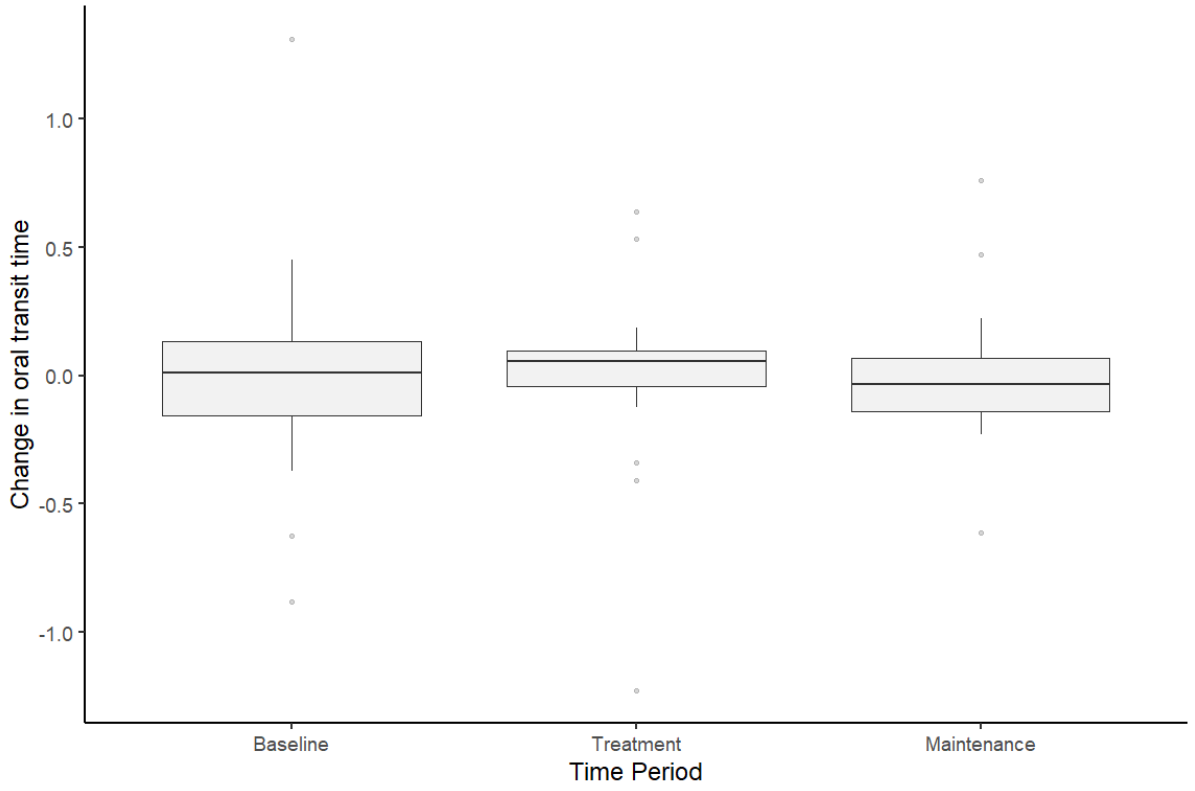


Note. Boxplot graph includes median, maximum and minimum change and inter quartile range.

Oral transit time measured by VFSS had significantly different rates of change between baseline and treatment time periods with liquid bolus trials (V = 9, p = 0.03). There was no significant change between treatment to maintenance time periods (V = 53, p = 0.08), or between baseline and maintenance (V = 19, p = 0.24). The distribution of the data represented in these results are summarised in Figure 8.4.

Figure 8.4

Summary of Oral Transit Time Rate of Change Across Time Periods



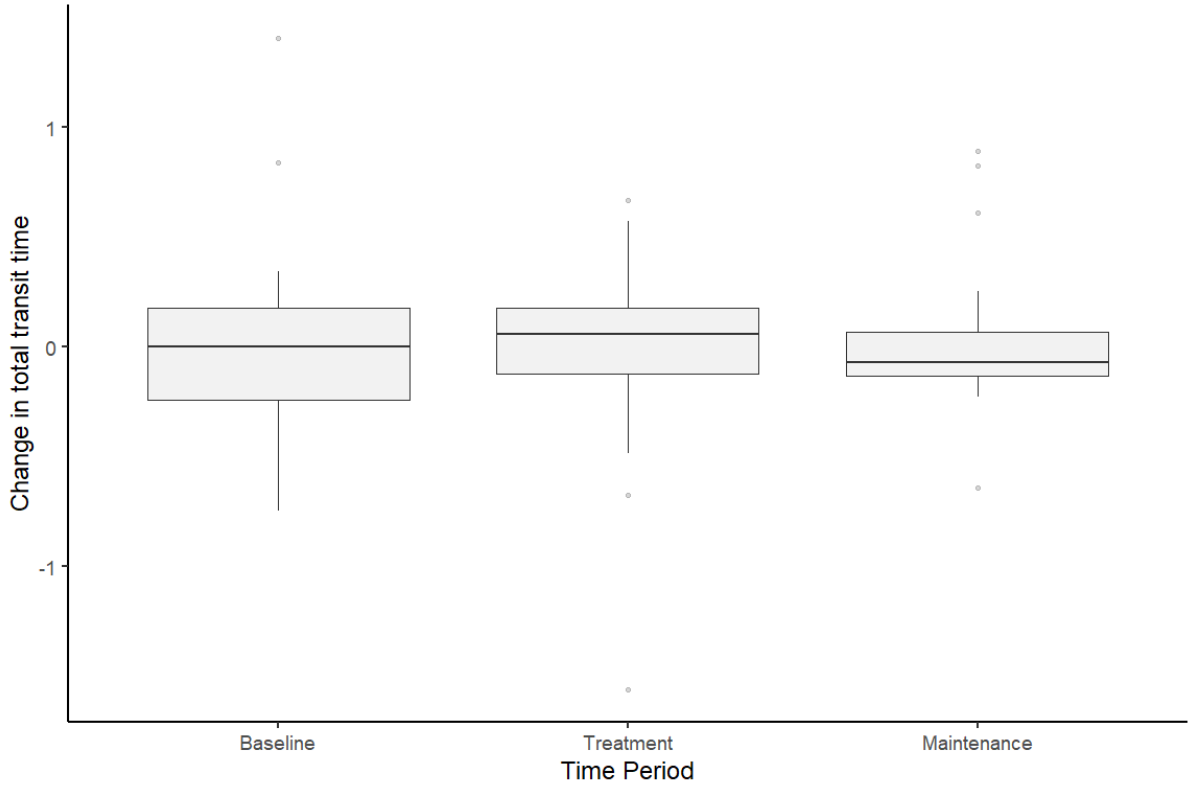
Note. Boxplot graph scaled to include outliers denotes the median, maximum and minimum change and inter quartile range of each time period.

The rate of change was significantly different for total transit time on liquid bolus during treatment compared to baseline periods: (V = 11, p = 0.05) and between treatment and

maintenance (V = 58, p = 0.02). There was no significant difference between baseline and maintenance (V = 28, p = 0.70). Total transit time rate of change increased during treatment and a decreased during maintenance time periods. This distribution of total transit time data is represented in Figure 8.5.

Figure 8.5

Summary of Total Transit Time Rate of Change Across Time Periods



Note. Boxplot graph scaled to include outliers denotes the median, maximum and minimum change and inter quartile range of each time period.

8.2.5 Variability Within Sessions

To evaluate variability within sessions, the SD was calculated for each outcome measure which included more than one swallowing trial. This new data set represented the within-subject variability compared across sessions. All data met the model assumptions of normality and

homoscedasticity. Variability analysis results are summarised in Table 8.11. There were no significant differences between the variability (SD) of any swallowing outcome measures as measured via US of VFSS ($p > 0.05$). One out of five LRM swallowing outcomes had significantly lower variability of UES minimum pressure across puree bolus trials in pre-therapy Assessment 2 compared to baseline Assessment 1 (- 4.96 mmHg (95% CI [- 9.08, - 0.84], $p = 0.01$).

Table 8.11

Variability Within Sessions of Outcome Measures with Multiple Trials

Assessment	Outcome Measure	Bolus	Chi-Squared (df)	*p* - value
Ultrasound	Percentage change (%)	Dry	χ^2 (3) = 1.79	0.62
		Liquid	χ^2 (3) = 1.73	0.63
		Puree	χ^2 (3) = 4.81	0.19
Videofluorscopic Swallowing Studies	Oral transit time (s)	Liquid	χ^2 (3) = 0.23	0.97
		Puree	χ^2 (3) = 1.48	0.69
	Pharyngeal transit time (s)	Liquid	χ^2 (3) = 2.04	0.56
		Puree	χ^2 (3) = 2.85	0.41
	Total transit time (s)	Liquid	χ^2 (3) = 1.87	0.60
		Puree	χ^2 (3) = 1.90	0.59
	Timing of supraglottic closure (s)	Liquid	χ^2 (3) = 2.92	0.40
		Puree	χ^2 (3) = 3.05	0.38
	Duration of aryepiglottic closure (s)	Liquid	χ^2 (3) = 5.45	0.14
		Puree	χ^2 (3) = 1.07	0.78
	UES duration open (s)	Liquid	χ^2 (3) = 0.30	0.96
		Puree	χ^2 (3) = 1.75	0.63
	UES distension (mm)	Liquid	χ^2 (3) = 1.06	0.79
		Puree	χ^2 (3) = 2.26	0.52

	Pharyngeal constriction ratio (PCR)	Liquid	χ^2 (3) = 3.87	0.28
		Puree	χ^2 (3) = 3.03	0.39
	Hyoid excursion (mm)	Dry	χ^2 (3) = 1.87	0.60
		Liquid	χ^2 (3) = 6.15	0.10
		Puree	χ^2 (3) = 3.05	0.38
Low Resolution Manometry	Sensor 1 peak upper pharynx (mmHg)	Dry	χ^2 (3) = 2.18	0.54
		Liquid	χ^2 (3) = 4.06	0.26
		Puree	χ^2 (3) = 2.04	0.56
	Sensor 2 peak mid pharynx (mmHg)	Dry	χ^2 (3) = 0.88	0.83
		Liquid	χ^2 (3) = 3.76	0.29
		Puree	χ^2 (3) = 2.97	0.40
	Peak to peak time (s)	Dry	χ^2 (3) = 3.58	0.31
		Liquid	χ^2 (3) = 3.12	0.37
		Puree	χ^2 (3) = 2.04	0.57
	UES minimum pressure (mmHg)	Dry	χ^2 (3) = 3.30	0.35
		Liquid	χ^2 (3) = 1.94	0.59
		Puree	χ^2 (3) = 12.68	0.005*
	UES open duration (s)	Dry	χ^2 (3) = 2.34	0.51
		Liquid	χ^2 (3) = 0.24	0.97
		Puree	χ^2 (3) = 0.36	0.95

8.2.6 Treatment Study: Case Study

Participant 4, a 30-year-old female, completed all assessments and treatment sessions within the specialist University research laboratory setting. She presented with Stage II HD (early to mid-stage), a MoCA score of 27 indicated cognition within normal limits. She could travel independently but required some assistance to plan the journey. She was unable to obtain employment predominantly due to motor impairments largely characterised by hyperkinetic movements. This included excessive tongue pumping and involuntary choreic movements of

her face, tongue and limbs. Her self-reported dysphagic symptoms (EAT-10 = 5) included increased incidents of coughing and choking episodes over the last 12 months during mealtimes plus the sensation of food and tablets 'sticking in my throat'. Frequent burping and reported aerophagia were noted during all sessions.

8.2.6.1 Task Performance

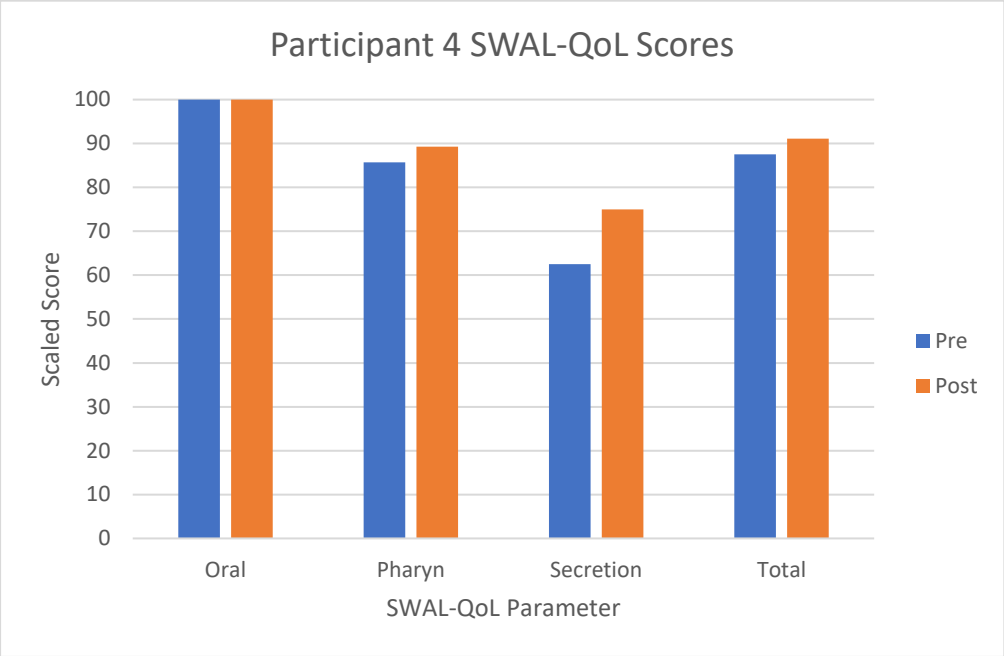
Participant 4 was able to complete the task despite notable oral choreic movements and tongue pumping. Participant 4's performance improved across the ten treatment sessions. Timing error decreased from 2.69 s to 2.25 s, amplitude error decreased from 42.70 μV to 19.02 μV and total error decreased from 103.52 mm to 38.3 mm from week 1 to week 2 of therapy.

8.2.6.2 Treatment Effect

As reflected in the group analysis, there were improvements in self-reported swallowing related QoL for this participant. Figure 8.6 depicts Participant 4's the SWAL-QoL scores pre- and post-therapy. An increase in score reflected an increase in perceived QoL for that parameter.

Figure 8.6

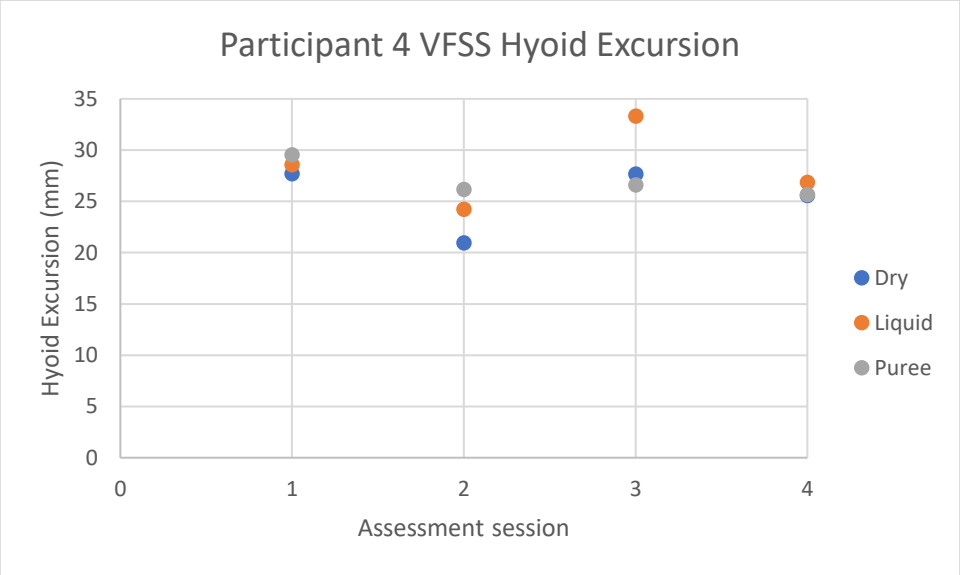
Individual SWAL-QoL Scaled Scores Pre- and Post-therapy



There were no notable differences in the performance of Participant 4 during the TWST or TOMASS assessments. Participant 4 completed the TWST with 30 swallows in 15 s pre-therapy and 16 s post-therapy. This then reduced to 24 swallows in 15 s in the final maintenance assessment which represented a small increase in volume and capacity during the post-therapy no-treatment phase. Participant 4 completed the TOMASS with the same number of bites (3) and swallows (2) across all assessments. The number of masticatory cycles increased from 35 pre-therapy to 38 post-therapy, but the time taken to complete the task reduced from 58 s pre-therapy to 51 s post-therapy. The measures of the submental muscles at rest via US were consistent in this case study. US measurement of hyoid excursion (percent change) decreased by 4% across all bolus types. In contrast, VFSS measurement of hyoid excursion represented in Figure 8.7, increased over the treatment period, but did not represent any clear trend over assessment sessions.

Figure 8.7

Participant 4 Hyoid Excursion Measured via VFSS Across Assessment Sessions

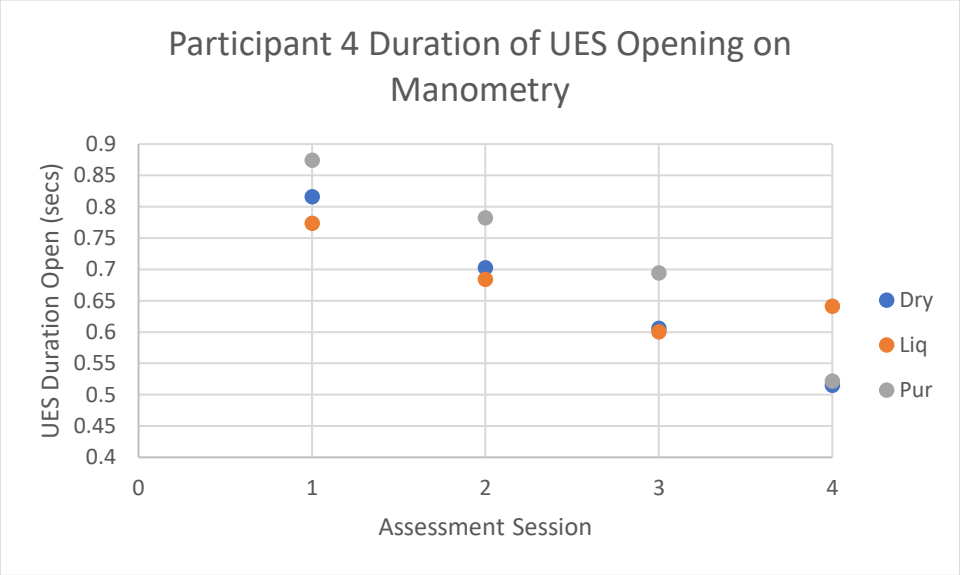


A significant treatment effect of UES distension was found on analysis of the group data; however, this significant reduction was not seen in Participant 4, who had an increase post-treatment (7.85 mm to 8.39 mm). Of the six timing measures obtained via VFSS, Participant 4 had longer oral transit times post-therapy (0.46 s to 0.56 s), which was reflected in the longer total transit time (0.9 to 1.00) and was significantly different as part of the group analysis. The duration of aryepiglottic closure was shorter in Participant 4 (1.02 s pre-therapy to 0.56 s post-therapy).

There were no identified trends in manometric measures of pharyngeal pressures for Participant 4 pre- and post-therapy; however, changes in manometric timing measures were noted. Peak to peak latency increased in from 0.08 s pre-therapy to 0.15 s post-therapy, and the duration of UES opening reduced across all assessment sessions, as presented in Figure 8.8.

Figure 8.8

Participant 4 UES Duration Opening Time (s) Across all Assessments as Measured with LRM

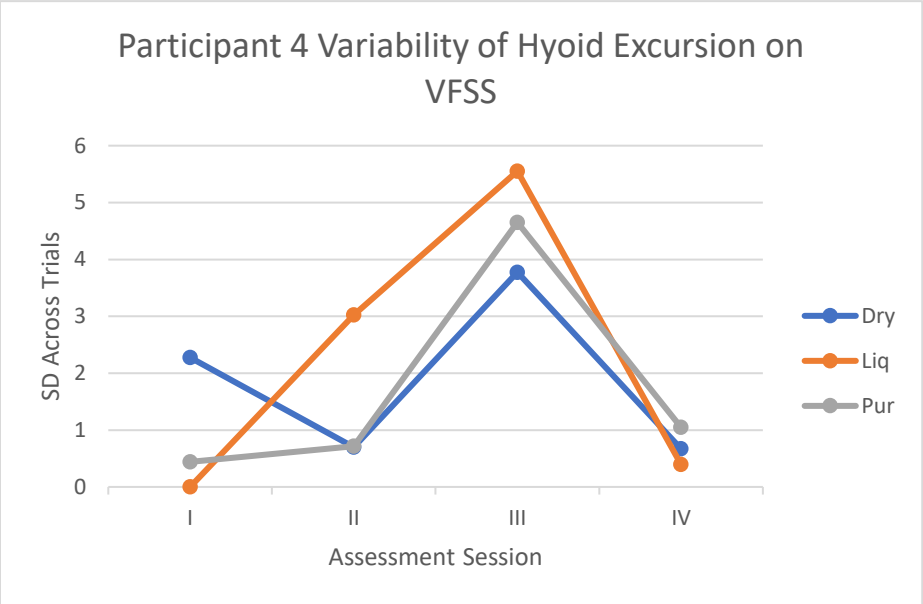


8.2.6.3 Variability Within Sessions

Group analysis of variability within sessions elicited no significant treatment effects. On further evaluation of individual variability, there were no identified trends in hyoid excursion measured by US for Participant 4. There were, however, differences noted for VFSS measurements of hyoid excursion. As depicted in Figure 8.9, variability of hyoid excursion measured with VFSS increased for Participant 4. There were no other trends noted in manometric variability.

Figure 8.9

Summary of Changes in VFSS Hyoid Excursion Variability Across all Assessment Sessions for Participant 4



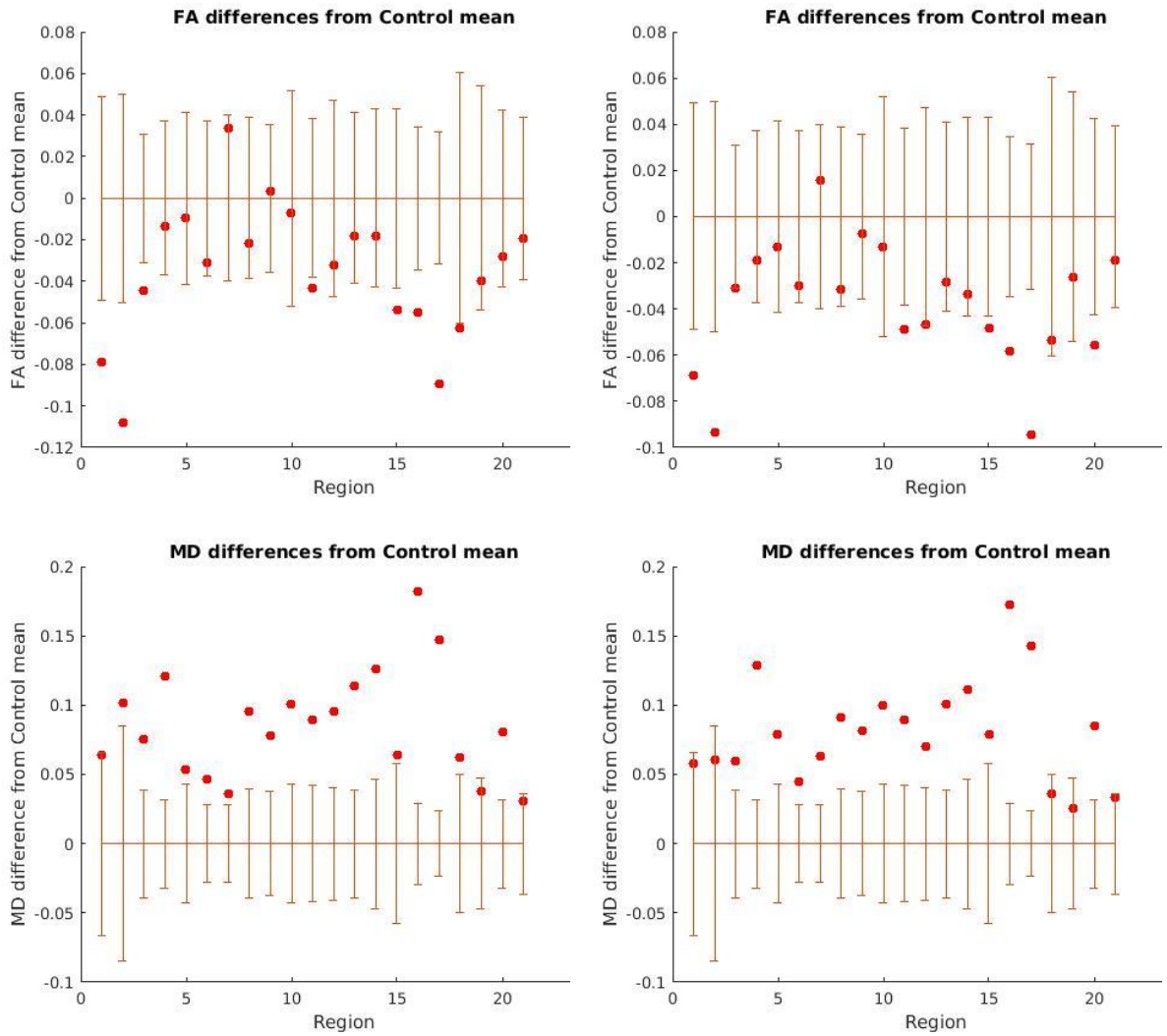
8.2.6.4 MRI Analysis

On pre-treatment evaluation, Participant 4 showed widespread cortical atrophy and fractional anisotropy (FA) values > 2 SD outside of the normal range were observed in 8 of the 21 regions of interest. One region, the splenium of the corpus callosum moved within the normal range post-treatment. Nineteen of the 21 regions of interest fell > 2 SD outside of the normal range as quantified by mean diffusivity (MD) values pre-treatment. Post-treatment, two regions reduced to move within normal range; these included the body of the corpus callosum and right cingulum. Differences in FA and MD pre-treatment and post-treatment are depicted in Figure 8.10.

Figure 8.10

Differences in Fractional Anisotropy (FA) and Mean Diffusivity (MD) Between Pre-treatment and Post-treatment.

Pre-treatment | Post-treatment



Note. Error bars represent 2 SD from the mean of the normative control data. This Figure was produced by Dr Nadia Borlese as part of the MRI report.

This results chapter quantifies the test-retest reliability and variability of multiple swallowing outcomes measured via behavioural and instrumental assessments. The results of the treatment study including the descriptive case study presented limited evidence to suggest clinically significant treatment effects following the skill-based dysphagia training.

Chapter 9: Discussion

There is a tendency for patients with HD, and other neurodegenerative disorders, not to be referred for instrumental swallowing assessment such as VFSS (Pizzorni et al., 2020). Despite the high prevalence of dysphagia, there is a lack of instrumental assessment data available to quantitatively measure swallowing features in HD (Pizzorni et al., 2020). This is the first research programme to evaluate test-retest reliability of swallowing measures in individuals with HD and apply these findings to the investigation of the feasibility and effectiveness of a novel skill-based swallowing training protocol with this patient population.

9.1 Test-retest Reliability of Swallowing Outcome Measures in HD

Assessment of swallowing is limited by inconsistent implementation of assessment methods which can lead to inaccurate interpretation and prevent comparisons between outcomes of intervention studies. The majority of existing dysphagia literature in HD relies on bedside clinical examination, which is difficult to reliability quantify (Pizzorni et al., 2020). Further, to trust the accuracy of swallowing outcomes, it is integral to evaluate and report the reliability of assessment methods. This test-retest study quantifies the reliability and variability of a wide range of swallowing outcome measures across sessions in patients with HD. In addition, careful evaluation of this reliability of standardised assessment methods can be applied to power calculations for subsequent intervention studies. This is important to ensure that any significant differences in outcomes can be more confidently attributed to treatment effects and not measurement error.

9.1.1 Reliability and Variability of Behavioural Outcome Measures

Swallowing outcome measures obtained from behavioural assessments, such as the TWST and TOMASS, are accessible, replicable and objective measures of liquid and solid bolus ingestion. These behavioural assessments demonstrated low estimated change across sessions (defined as variability) and good to excellent test-retest, intra-rater and inter-rater reliability in this patient group. This reliability in HD is relatively consistent with other literature (Huckabee et al., 2017; Hughes & Wiles, 1996; Nathadwarawala et al., 1992); there were however, certain parameters of the TWST and TOMASS which demonstrated lower reliability in our HD patient population compared to normative data (Huckabee et al., 2017; Hughes & Wiles, 1996). Of the three TWST measures, time per swallow had the lowest reliability. As this measurement required additional rater observations (number of swallows and time taken) to obtain the results, these combined elements may be difficult to reliably judge in patients with HD. In contrast, this timing measure of the TWST was the least variable across sessions. The variability in swallowing capacity and volume between the first assessment and subsequent sessions is comparable to differences reported by Hughes and colleagues (1996) in healthy subjects.

Oral phase outcomes of the TOMASS such as number of bites and number of masticatory cycles resulted in the poorest test-retest reliability. This may be indicative of motor sequencing impairments, irregular motor patterns and self-feeding difficulties associated with basal ganglia dysfunction in HD. Despite moderate to good reliability, the number of swallows and total time of the TOMASS were most variable across sessions. Of note, the estimated change for both of these outcomes decreased between the first and subsequent assessments which is consistent with trial and session effects reported by Huckabee and colleagues (2017). The reduction in time taken to complete the TOMASS in this HD group may reflect participant familiarity with the task as low variability (< 1%) was recorded between the second and third assessments. This

session effect and reduced variability of performance must be considered during re-assessment post-intervention to ensure these habitual improvements are not attributed to treatment effects.

9.1.2 Huntington's Disease Characteristics Which Influence Reliability of Swallowing Measures

9.1.2.1 Influence of Motor Impairments

There are several elements of HD pathophysiology which can impact on the reliability of measurement. Individual HD characteristics such as trunk hyperextension, involuntary movements of the head and limbs, and lingual chorea may have had an adverse effect on reliability of instrumental outcomes. Symptoms such as lingual chorea and tongue pumping were important to note as they have been correlated with increased risk of aspiration (Schradt et al., 2018). Although choreic movements were observed both at rest and during dynamic movements, the reliable identification and selection of volitional swallowing events was more affected by these atypical motor behaviours. This was evidenced as dynamic swallowing measures such as hyoid excursion measured with VFSS and US had poorer test-retest reliability compared to measures of anatomical structures at rest. Measures such as the cross-sectional area of the submental muscles measured via US which did not require the participant to swallow, and did not require visualisation of moving anatomical features, demonstrated the highest reliability and lowest variability in this HD cohort.

Difficulty in controlling for involuntary head movement during VFSS, has likely contributed to poor reliability and increased variability observed. It is important to consider that measurement of hyoid excursion obtained via VFSS may not reflect the true trajectory or displacement of the hyoid bone if the head is rotated out of the optimum plane. In contrast, the handheld US devices provided flexibly for the investigator to follow the participant's choreic

head movements to ensure the anatomical reference points were captured within the optimum frame, consistent with previous evaluation of handheld devices (Perry et al., 2016). Although no patient studies investigating US assessment of swallowing have previously included individuals with HD, the test-retest reliability in our HD cohort reflected relatively comparable patterns of reliability to previous research (poor for hyoid excursion, moderate to excellent for cross-sectional area of the submental muscles) (Shimizu et al., 2016; Winiker, 2019).

The test-retest study included individuals at different stages of HD; it is difficult to define the influence of mixed hyperkinetic or hypokinetic motor impairments which could have influenced the reliability and variability of results. Test-retest reliability data from the spinal literature has reported significantly reduced reliability when assessing individuals with early HD compared to later stages (Quinn et al., 2013b). This may suggest that the highly variable between-participant motor responses associated with different stages of HD have likely contributed to lower reliability demonstrated in our study. Evidence suggests that individuals with HD are unable to consistently adapt or regulate their swallowing response based on sensory stimuli (Kagel & Leopold, 1992). Therefore, increased variability during bolus trials may represent the disrupted cortical and striatal feedback loops in HD. Swallowing biomechanics in HD may be irregular and poorly coordinated, characteristic of ataxic-type movement patterns, which are more variable during voluntary bolus trials. Inconsistent and uncoordinated swallowing biomechanics with involuntary movements both within and between subjects is likely to contribute to the reduced reliability of VFSS and LRM measures.

9.1.2.2 Combined Influence of Motor and Cognitive Impairments

In addition to the motor impairments which impact data acquisition, the increased cognitive demands of the assessment procedure could have influenced individual performance.

Combined assessment procedures such as manofluoroscopy placed high task demands on the participants to swallow on cue with a catheter placed, whilst coordinating self-feeding and maintaining an optimum position. During complex psychometric tasks which placed similar demands on dual motor and cognitive processing, patients with HD have demonstrated reduced task performance and compensatory recruitment of additional cortical regions (Andrews et al., 2015; Soloveva et al., 2018). Perhaps the additional processing demands during self-feeding contributed to inconsistency of ingestive swallowing modulation and programming. This could explain the difference in variability of hyoid excursion comparing measurements obtained via VFSS and US. The more cognitively demanding VFSS procedure had higher variability of the motor response compared to lower demand US. The distinction between reliability of US rest measures and displacement measures may also suggest that increased involuntary or irregular motor responses were associated with increased task and processing demands (Novak & Tabrizi, 2010). Previous research evaluated the variability of these US measures in healthy participants; the maximum variability across sessions was 6% for hyoid displacement (Perry et al., 2016). The variability of hyoid displacement with HD patients was comparatively higher than that reported in healthy participants, consistent with the irregular motor response observed in other results. Hyoid percentage change across subjects varies in healthy participants; Macrae et al (2012) reported a range of 17% to 44% in hyoid displacement from five swallows in five healthy participants. As these studies in healthy participants reported high within-subject and between-subject variability, one would expect this variability to be higher in this complex and changeable patient cohort.

In addition, LRM measures indicated that sequencing of the pharyngeal response had high variability and low reliability across sessions in this HD group. Variability of LRM within and across sessions has been previously evaluated in healthy participants (Macrae et al., 2011). In

this cohort of 20 healthy people, Macrae et al. (2011) reported a maximum 12% estimated change of peak or nadir pressures (mmHg) at Sensors 1, 2, and 3 across sessions. Our test-retest study exceeded this 12% estimated variability in 12 out of 18 LRM measures in individuals with HD. The highest variability at Sensor 1 was during liquid bolus swallows. As Sensor 1 is located in the proximal pharynx around BoT perhaps this high variation with bolus swallows is consistent with the VFSS findings above. It may reflect disorganised or abnormal initiation of the pharyngeal motor programme in response to bolus stimulus, compared to self-cued initiation of the dry swallows. There could also be an influence of lingual chorea or involuntary movements of oropharyngeal muscles during bolus preparation. Although one may have expected to see more lingual struggle during initiation of dry swallows at Sensor 1, the introduction of the liquid bolus resulted in a more variable response. This is also consistent with several reports that thin liquid is the most difficult bolus consistency for those with HD to control (Leopold & Kagel, 1985; Trender-Gerhard et al., 2016). In contrast, the duration between peak pressures at Sensor 1 and Sensor 2 demonstrated higher variability with dry swallows across all sessions. Whilst this could have highlighted poor reliability of this measurement, these results may also suggest altered biomechanics and specifically incoordination of swallowing timing with a more tense, conscious, cortically driven pharyngeal response. As all individuals in this group were able to eat relatively normal diet, we are unlikely to have captured more severe dysphagia. The variable biomechanics may indicate an early maladaptive response to maintain function and compensate for corticostriatal pathway disruption as suggested in the corticospinal HD literature (Klöppel et al., 2009). However, further research is needed to investigate how these early changes manifest in corticobulbar symptoms such as dysphagia.

9.1.2.3 Influence of Measurement Error

The test-retest reliability of these specific assessment methods is not clearly documented in the literature; however, the low reliability of instrumental assessment measurements in HD patients may suggest the individual's inconsistent motor responses were likely to influence measurement reliability. Additionally, the precision and technical aspects of manofluoroscopy combined with this challenging disease may have increased the risk of measurement error. Literature exists regarding normative data and variability of LRM (Butler et al., 2009; Lamvik et al., 2014; Macrae et al., 2011); however, the test-retest reliability of this assessment procedure has not been clearly defined. Despite following specified protocols described in other studies (Butler et al., 2009; Lamvik et al., 2014; Macrae et al., 2011; Salassa et al., 1998), this study demonstrated poor test-retest reliability in HD across all LRM parameters. The number of unidirectional markers was noted for each participant to ensure consistency of insertion depth across sessions, and catheter placement was confirmed radiologically. However, consistency of sensor positioning is an identified limitation of LRM (Huckabee et al., 2015), as the exact location of the sensors during swallowing could have differed across the three sessions.

There are several methods available to measure displacement and timing of swallowing from VFSS (van der Kruis et al., 2011). This study utilized the widely recognized Leonard and Kendall (2019) protocol which included several standardised timing and displacement swallowing measures. This resource provides descriptions and instructions to obtain the measurements from VFSS (Leonard, 2019a). Each measurement has respective inter-rater reliability data for healthy individuals and patients with dysphagia. Test-retest reliability of quantitative swallowing outcomes obtained via VFSS has seldom been reported in the literature. One study reported test-retest reliability of several methods to evaluate VFSS in 40

patients with head and neck cancer (Frowen et al., 2008); however, reliability was only evaluated across three swallows per bolus and did not include multiple sessions across time points as in our HD study. Frowen and colleagues (2008) reported inadequate test-retest reliability (ICC < 0.75) for 6 out of 7 timing measures of VFSS and poor to excellent reliability of displacement measures (ICC = 0.48 – 0.89). Both timing and displacement measures in our study had a mixture of poor to moderate reliability in HD. Of note, individual variability across different days in our test-retest study is likely to be higher with HD patients compared to one assessment session with head and neck cancer patients.

The VFSS data had highest variability between the first and second assessments on 6 of the 12 timing measurements. As difference between sessions was not reflected in the LRM data acquired on the same swallows during combined manofluoroscopy, this suggests that swallowing measures obtained by VFSS are more subject to variability in subsequent sessions compared to LRM measures. This could be due to a number of factors including the number of subjective judgements and measurement steps required by the raters to obtain the VFSS data. Test-retest variability of measures has not been reported using this VFSS protocol, however Kendall (2002) reported that the swallowing sequence of events in healthy adults (n = 60) differed across test-retest assessments with 30.5% of participants altering from the normal sequence of measures used in our study. The authors also observed higher variability of events during smaller bolus swallows (e.g. 1 ml and 3 ml compared to 20 ml). They hypothesised that larger bolus volumes resulted in faster bolus transit times and reduced behavioural variability in healthy individuals (Kendall, 2002). A difference in variability in bolus types was also noted with our VFSS data, however, Kendall et al.'s (2002) theory contrasts with our findings which included only 5 ml bolus trials. We found that pharyngeal transit time was less variable with higher viscosity puree swallows compared to liquid swallows. This trend was reflected in 6 out

of the 9 other timing and displacement measures. Hyoid excursion had the lowest variability with dry swallows, which again is the opposite of the expected contribution of large bolus volumes suggested by Kendall (2002). This increased variability in HD during liquid bolus swallows could be another example of imprecise or irregular motor patterns in response to a rapid bolus stimulus.

9.1.2.4 Influence of Rater Judgement

Evaluation of intra-rater and inter-rater reliability provides a foundation for interpreting the reliability of outcomes. There is, however, poor reporting of reliability across the literature and huge variation dependent on method and rater training. There are several sources of variation which may exist between raters (Molfenter & Steele, 2014), however studies seldom specify how the process of rater reliability was completed to allow for replication (Baijens et al., 2013a; Humbert et al., 2018; Leonard & McKenzie, 2006). Leonard and Kendall (2019) reported all timing and displacement measures derived from VFSS had excellent inter-rater reliability (ICC > 0.92) (Leonard, 2019a). Despite following the identical measurement protocol, inter-rater reliability was lower for the same measures in both HD studies. As the descriptions often included examples of normal swallowing, accurate replication was limited in patients with atypical swallowing behaviours. This may indicate inadequate description of the measurement protocol. Further evaluation and examples of these methods implemented with different aetiologies would improve rater understanding and measuring reliability.

Heemskerk et al. (2015) is the only study to detail timing measures of a group of HD patients and did not report inter-rater or intra-rater reliability results. Kagel and Leopold (1992) compared a similar spread of HD disease stages as in our studies and reported hyoid movement based on the average of 5 selected swallows with a 5 ml bolus. The authors only reported intra-

rater reliability (0.85 to 0.89), but the method was not described. Another study evaluating VFSS in HD report higher inter-rater reliability with subjective rating scales to judge the presence or absence of a swallowing symptom but failed to specify whether these ratings were made individually, or part of consensus (Keage et al., 2020). Subjectivity of rater judgements combined with rater experience could influence measurement reliability. This was evident for PAS ratings where differences in judgements of PAS 2 or PAS 4 were the predominant disagreements in the treatment study. Although the clinically significant judgement of presence of aspiration or penetration using the PAS is widely reported across the dysphagia literature, the reliability or absolute agreement between raters is often omitted. Despite several months of training and consensus meetings to review similar videos, this disagreement was still highlighted. Additional training resources with clear examples for interpretation of each level would be beneficial.

Our reliability included image selection from videos prior to measurement. The videos in this complex patient population often included extraneous movements and multiple swallows introducing additional judgements for raters to make prior to the measurement. Perhaps the inclusion of consensus discussions, exclusion of non-optimal videos, pre-selected images and analysis software may have increased our inter-rater reliability. Our protocol, however, maintained strict confidentiality between raters so the 20% sample was not discussed. The image selection and measurement instructions may have been differently interpreted by individual raters which represents true inter-rater reliability in this HD cohort. Studies reporting good to excellent inter-rater reliability of hyoid displacement reported re-assessment of pre-selected images (Sia et al., 2012) or exclusion of data if structural elements were not clearly visible which could introduce a selection bias (McCullough & Kim, 2013). A recent methodological study retrospectively evaluated VFSS images of dysphagic patients using four

methods to judge pharyngeal residue (Steele et al., 2020). The authors reported excellent reliability for all but one measure, similar to those reported by Leonard (2019a); however, it was highlighted that inter-rater reliability began by "resolving any differences across raters in selection of the swallow rest frame for the initial swallow" (Steele et al., 2020, p.1411). This process removed differences in frame selection, and by definition, removed levels of inter-rater variability. Unsurprisingly, the utilisation of semi-automated computational analysis to identify key points of frame by frame coordinates for VFSS has the highest reported rater reliability (Logemann et al., 2000; McKenzie & Leonard, 2019; Schwertner et al., 2016). Similarly, our LRM data was analysed by identifying target peak waveforms within the LabChart analysis software to extract data from the recordings. Excellent intra-rater and inter-rater reliability was demonstrated across all measures and across both studies which is consistent with other studies using LRM (Gumbley et al., 2008; Lamvik et al., 2015; Lan et al., 2012). Of note, LRM measures had poor test-retest reliability despite the excellent rater agreement which reflects the impact of within-subject variation in performance on reliability of this measure.

9.1.2.5 Influence of Data Acquisition During the Session or Offline

Recent research has suggested that test-retest reliability was lower when measurements were obtained online during the session (Hammond, 2019; Winiker, 2019). This is consistent with our findings in HD as US measurements obtained offline during the test-retest study were more reliable compared to online measurements obtained during the session. Inter-rater reliability of US was comparable to swallowing outcome measures in other neurodegenerative diseases such as PD (Hsiao et al., 2012; Oh et al., 2016; Shimizu et al., 2016). Evidence to suggest offline measurement increases reliability of US measures was further demonstrated as several US measures had a significant rating or rater effect using online data extraction as part of the test-retest study; however, there were no identified rater effects in the treatment study when the

measurements were obtained offline. The improved reliability in offline data extraction and measurement may reflect reduced environmental pressures, time constraints and improved technological environment for visualisation and accurate image selection. Additionally, inter-rater reliability was higher for the treatment study across all US measures which may reflect the additional experience of the second rater at the time of the final study.

9.1.3 Methodological Reliability Study Summary

Accurate and reliable assessment of swallowing biomechanics is crucial to diagnose and select appropriate interventions in individuals with HD. Objective assessments allow clinicians to quantify treatment effects and monitor natural changes across the course of the disease. Evaluation of reliability is a critical step in interpreting outcomes and evaluating any treatment effects. Lower reliability affects the accuracy of swallowing outcomes and interpretation of results. Despite the reduced reliability of instrumental measures in this population, the use of standardised measurement techniques can provide objective information to compare across studies. The results of this test-retest study can aid clinicians and researchers to critically evaluate the reliability of swallowing outcomes to extract clinically significant changes during review or following treatment. Although reliability of swallowing measures is problematic in this population, this is the first study to measure the average change (variability) across sessions of multiple swallowing outcome measures in HD patients. This information can be used to design future research, interpret clinically significant changes and is integral to distinguish typical patient behaviour from changes likely to be attributed to a treatment effect.

9.2 Treatment Study Discussion

This is the largest treatment study to evaluate skill-based dysphagia training secondary to neurodegenerative disease. In addition, it is the largest swallowing intervention study in HD to

include instrumental measures of swallowing biomechanics following specified protocols. This research builds on the findings of previous studies using the same skill-based training programme (Athukorala et al., 2014; Perry et al., 2018) and demonstrates that high intensity swallowing rehabilitation is safe, well-tolerated and feasible for people with neurodegenerative conditions. All participants completed all sessions and assessments. This excellent retention rate and adherence is higher than that reported in other treatment studies (Cruickshank et al., 2015; Easterling, 2013; Jones et al., 2016; Plowman, 2016). All participants in this treatment study complied with the intensity of the training protocol. Although task performance was not an identified outcome measure, all participants engaged in sessions and completed all 80 trials per session. This repetitive practice and focussed attempts to improve the accuracy of temporal and amplitude aspects of the motor response was the target of this skill-based swallowing training. This study provides evidence in support of the feasibility of daily home-based rehabilitation for treatment of dysphagia in HD as previously highlighted in other neurodegenerative diseases (Plowman et al., 2019).

9.2.1 Self-reported Quality of Life: Session Effects

There were significant improvements during treatment in self-reported swallowing QoL. The only parameter that did not change was specific to oral phase impairment. Oral phase impairment reported in the SWAL-QoL, such as difficulties with labial closure or mastication, were not directly targeted with this intervention. This skill-based training aimed to increase the conscious control of dry swallowing initiation. Additionally, symptoms included in the oral phase parameters such as drooling were not reported as significant issues in this cohort. These symptoms are often associated with cognitive impairment (Leopold & Kagel, 1997) and therefore were relatively mild in this group as part of the inclusion criteria. If the symptom was not present in this group pre-therapy, it would not be sensitive to improve with intervention.

These SWAL-QoL results are similar to the EMST RCT in HD which reported a moderate positive effect on swallowing QoL in the HD group and a small positive effect on the control group. Our results are also consistent with improved QoL following skill-based dysphagia therapy in individuals with PD (Athukorala et al., 2014; Curtis et al., 2020a). The participants of these treatment studies were unable to be blinded to the timing of their SWAL-QoL ratings, and in our study, the questionnaire was given directly to the investigators. Although participants were unlikely to remember their responses from the previous assessments, there may be a risk of reporting bias or a participation effect as noted in Reyes et al. (2015), as their participants reported positive improvements following both active and sham intervention.

9.2.2 Behavioural Aspects of Swallowing: Session Effects

Individuals reported perceived functional improvements in drinking fluids which was not reflected in the behavioural deglutitive outcomes. There were no significant differences in the group data across assessment time points for any behavioural outcome measures. Although this implies an absence of treatment effects, there was some noted reduction or elimination of overt signs of aspiration when the TWST was completed post-therapy. Assuming that the treatment did not change laryngeal sensitivity, this could indicate an improvement in swallowing safety during sequential water swallowing which was not picked up by other parameters of the TWST or the VFSS outcomes measures. Additionally, other studies have reported the TWST as a sufficiently sensitive assessment to highlight change in HD after four months of intensive training (Reyes et al., 2015). Although non-significant increases in the time taken to complete the TOMASS were observed during the baseline and treatment time periods, this was the only outcome which significantly reduced during the maintenance period. These behavioural swallowing outcomes demonstrated low variability and high reliability in the test-retest study; however, as none of the other behavioural measures changed, this decrease in TOMASS time

is unlikely to reflect a delayed treatment effect. This treatment study showed no significant reduction in functional ability to complete these ingestion tasks across the six weeks; however, no significant deterioration was observed during the baseline control period which suggests this group was relatively stable. Therefore, despite patient perceptions, there is no evidence to suggest this treatment protocol had any effect on behavioural ingestion of liquids or solids.

9.2.3 Timing Outcomes: Session Effects

The differences in reliability of these assessment methods was evaluated in the test-retest study and likely contribute to the conflicting hyoid excursion results. Quantitative VFSS outcome measures have never been conducted to evaluate treatment effects in HD; is it therefore difficult to compare our results to other intervention studies. Oral and pharyngeal bolus transit times were longer post-therapy which resulted in a significant treatment effect on total transit times with liquid bolus only. Interestingly, puree bolus transit times were shorter post-therapy across all timing measures, but this difference did not reach significance. This is the opposite of longer swallowing times with thicker textures reported in healthy participants (Steele et al., 2019). As rapid swallowing and shorter oral transit times have been previously reported in HD with liquid bolus swallows (Hamakawa et al., 2004; Heemskerk et al., 2015), the potential of treatment to improve bolus transit times in HD could be of clinical significance worthy of further investigation. However, the timing measures for liquid swallows in this study appear unstable and significantly declined during the baseline period of no-treatment then significantly increased during treatment. Whilst this significant improvement may indicate more consciously controlled motor programmes for thin liquid swallowing in HD, it is difficult to determine clinical significance from these results. These VFSS timing measures demonstrated poor reliability and as this observation was only with liquid bolus it is more likely to represent

variability of the outcome measure instead of a significant treatment effect on swallowing biomechanics.

Additionally, no significant treatment effects were identified immediately post-treatment from manometric results which suggests that this treatment protocol did not induce changes as measured by LRM. In contrast, significant changes were observed in the final assessment session two weeks after cessation of treatment. Average peak to peak duration with puree swallows, pressures in the hypopharynx during dry and liquid swallows and UES opening duration all significantly decreased and moved towards normative data (Lamvik et al., 2014), consistent with a less effortful motor response (Hiss & Huckabee, 2005). Pharyngeal pressure peak to peak sequencing was shorter in this HD group compared to normative data (average 150 ms and 239 ms, respectively) (Huckabee et al., 2014); however, this pharyngeal mis-sequencing was not as impaired as patients with acute neurogenic dysphagia described by Huckabee and colleagues (2014). Mis-sequencing was unlikely to change over two weeks of this skill-based treatment which did not provide specific biofeedback to visualise pharyngeal sequencing. As the LRM results demonstrated high variability between sessions as reported in the test-retest study, we are unable to conclude that significant differences identified during the maintenance period suggested any evidence of a delayed treatment effect. As other studies have reported significant effects of catheter location and condition of swallowing (Hiss & Huckabee, 2005), the differences specifically seen during the final assessment period may indicate measurement error or a difference in catheter placement during this session.

9.2.4 Peripheral Displacement Outcomes: Session Effects

The second treatment effect included a significant reduction in UES distension which was not maintained post-therapy. Again, one could hypothesise that this represents improved efficiency

of the swallowing motor programme not to 'overshoot' the UES opening in response to a puree bolus (Gordon et al., 2000). However, as no other treatment effects were observed in swallowing biomechanics, perhaps this is more reflective of a measurement error. Further, as this submaximal skill training did not aim to increase muscle bulk through peripheral muscle strengthening, the absence of change in the cross-sectional area of the submental muscles as measured by US was expected.

Evaluation of hyoid excursion provided an interesting comparison between US and VFSS measurements. Although no significant treatment effects were identified, the outcomes were contradictory between the two assessment techniques. There was a significant decrease in hyoid excursion during dry swallows measured via VFSS during the baseline period. This decrease during a time of no treatment could indicate a natural decline which was halted through intervention and maintained post-therapy. As this decline was not noted for the other bolus types, perhaps this indicates task generalisation and improvement in dry swallowing biomechanics which are not included in the other VFSS measures. Alternatively, with consideration of the test-retest study results and low reliability of many VFSS outcome measures, we are unable to assume that this one significant anomaly has any clinical significance in this treatment study.

Despite the two significant treatment effects, there was an overall lack of evidence to suggest this training protocol changed swallowing safety or biomechanics in this HD cohort. However, other studies have reported functional improvements in swallowing post-therapy which were not reflected in instrumental outcomes (Cabib et al., 2020; Sdravou et al., 2012; Steele et al., 2013). In strength training RCT studies in MND and PD (Plowman-Prine et al., 2009; Troche et al., 2010), there were no significant improvements in VFSS measures after four to eight

weeks of intervention; however, both studies reported significant deterioration in the control groups. The baseline period is our HD study was designed to be a within-subject control group. As there was a lack of significant decline across baseline and treatment periods is suggests stability of swallowing in this patient group. We are therefore unable to conclude that treatment prevented further deterioration of swallowing in this neurodegenerative group.

9.2.5 Swallowing Safety: Session Effects

This is the first treatment study to compare PAS ratings pre- and post-swallowing rehabilitation intervention in HD. Of note, 97.85% of swallowing events over all four assessment sessions were scored as either PAS 1 or 2 in this study. This is comparative to normative PAS ratings reported in healthy adults (Humbert et al., 2018; Steele et al., 2019). PAS > 2 was only observed in liquid bolus swallows. Deeper penetration reaching the level of the vocal folds before clearing was not observed immediately pre-therapy but occurred on three occasions post-therapy, which could indicate deterioration in swallowing safety.

Two studies have reported penetration or aspiration from VFSS in relatively large HD cohorts. Heemskerk (2015) reported 12.1% of patients with HD (n = 45) either penetrated or aspirated on 5 ml thick liquid bolus at one time point; however, the PAS was not used to quantify the laryngeal response during VFSS and cannot be compared to our data. In another study, no timing or displacement measures were obtained from VFSS data with HD patients (n = 49), however PAS ratings were reported (Keage et al., 2020). No treatments were implemented, but seven patients underwent repeat VFSS at highly varied time points ($\bar{x}$ = 652.57 days, range 231–1115 days). Keage and colleagues (2020) reported high variability of PAS ratings with individuals ranging from PAS score of 8 to PAS score of 1 and PAS score of 1 to PAS score of 7 across time points. These findings highlight concerns regarding the sensitivity and

reliability of this outcome in individuals with HD. Although our patient cohort had longer symptomatic disease duration ($\bar{x}$ = 10.58 years) compared to Keage and colleagues (2020), ($\bar{x}$ = 7.76 years), our patient sample had functionally intact or relatively mild swallowing dysfunction resulting in fewer incidents of aspiration or penetration. Neither of these studies reported the protocols of how swallowing safety was analysed (i.e. how many trials were scored, how many trials of each bolus, how the PAS was obtained). Furthermore, both studies reported the mean PAS ratings which are unsuitable for this rating scale and limits comparison between studies (Borders & Brates, 2019). Due to the relatively normal incidents of penetration observed across this small sample, this rating scale may not be sensitive to change (Steele & Grace-Martin, 2017). We therefore cannot conclude that this treatment protocol had any effect on swallowing safety.

9.2.6 Neural Connectivity: Treatment Effect

The single case study provided the first preliminary MRI data to explore the effect of skill-based dysphagia therapy on neural connectivity compared to a healthy control. As this did not include baseline or maintenance effects, results cannot be generalised. However, in this neurodegenerative disease where cortical atrophy is present before motor symptoms, any changes identified on MRI may be clinically significant. Despite the diffuse neural degeneration reported for Participant 4, functional changes in swallowing were observed in the descriptive case study post-treatment. This skill-based dysphagia training which aimed to increased cortical connectivity and downflow resulted in significant improvements to the right cingulum and two regions of the corpus callosum. These regions are highly connected to the cingulate gyrus which has been associated with voluntary swallowing tasks (Martin et al., 2001), and show increased activation in mildly dysphagic HD patients (Michou et al., 2017). In addition, the right cingulum has been identified to strongly relate to cognitive abilities

(Bathelt et al., 2019) which may indicate increased cognitive processing and attention during motor learning tasks consistent with improved conscious control to adapt the motor response. The changes in two of the three regions of the corpus callosum could suggest improved interconnections between the two cerebral hemispheres, specifically BA 44 (Broca's area) which is critical for motor planning (Seikel et al., 2020). Although the three quantifiable improvements to bilateral white matter integrity in HD indicates the presence of neuroplasticity in response to intensive rehabilitation (Soloveva et al., 2018), it is important to recognise that 16 other regions of interest did not significantly change post-therapy. As reflected in other outcome measures, the changes in this small sample are interesting, provide important preliminary data to support further research, but do not represent any clear clinical significance following this treatment protocol.

Our results may also reflect findings that HD patients with severe dysphagia had cortical atrophy in associated deglutitive regions, not regions specifically associated with HD pathophysiology (Schumann et al., 2018). Further, other studies have reported quantifiable neural changes within the motor cortex in response to swallowing rehabilitation which did not translate to observed treatment effects in VFSS measures of swallowing biomechanics (Cabib et al., 2020). In HD, the general striatal and cortical damage and deterioration may be well established, but the occurrence and severity of dysphagia does not clearly correlate with disease severity or other clinical features. Perhaps pre-morbid organisation and tomography, not disease stage, influences susceptibility to neuroplasticity through rehabilitation as suggested in recovery of swallowing post-stroke (Wilmskoetter et al., 2020). This may explain why some participants demonstrated functional improvement whilst others did not, and presents an interesting area requiring further research in neurodegenerative populations like HD.

9.2.7 Rate of Change

Guidelines for optimum study design in HD research suggest a treatment effect should be considered as percentage reductions (20%) in the mean rate of change compared to healthy controls (Frost et al., 2017). Whilst we were unable to compare our results to healthy controls due to the adoption of different bolus presentation protocols, it was hypothesised that the greatest rate of change would be observed during the treatment phase compared to baseline. One parameter of the SWAL-QoL demonstrated significantly higher rate of change during the treatment phase. This observation relating to the participants' perception of having thick or excess secretions may indicate generalisation of the daily task to repeatedly complete dry swallows during sessions. Highly significant differences in the rate of change for oral transit time measured by VFSS contributed to significant differences in total transit time during the treatment period. The mean rate of change (18.39%) for oral transit time was higher than the maximum variability (12.5%) reported in the test-retest reliability study. As indicated with the transit time treatment effects, these data provide preliminary evidence that skill-based treatment may alter the timing of swallowing initiation and transit in this group. However, from observation of these results in boxplots (Figures 8.4 and 8.5, p.198-201), the means do not appear significantly different. These results, therefore, should be interpreted with caution. The results and R-coding were re-checked by the statistician familiar with this data set. There are no obvious explanations for this, and further replication of this research should investigate this anomaly. Additionally, these were the only identified parameters to change, so it is difficult to conclude that the treatment has a clinically significant difference in the trajectory of change in this neurodegenerative disease.

9.2.8 Variability of Outcomes

An alternative means of analysing the data to investigate any treatment effect was to evaluate changes in variability across sessions. Variability in the precision and force of movements has been correlated with functional capacity and motor performance suggesting that variability is a key feature of the motor deficits in HD (Gordon et al., 2000). Unfortunately, this hypothesis was not supported by the data. Variability of UES minimum pressure as measured by LRM significantly reduced during the non-treatment baseline period only. Resting pressure of UES is highly variable dependent on motor neurone activation from NA, additionally head and neck postures can change UES pressures (Massey, 2013). Although significant, this UES variability falls within the 95% confidence intervals observed in test-retest estimated change for the same measure. This could reflect positioning differences across sessions, the familiarity and relaxed approach for the second assessment session; however, no other sensors had significantly reduced pressures during this time period. This result was not clinically significant and likely reflected natural variability of this measure in this population. Improved or reduced variability during the treatment phase may have suggested a more consistent motor program as hypothesised from the corticospinal literature. There were no other differences in variability across other measures, therefore there was no evidence that this skill-based training protocol induced any change in the variability of swallowing biomechanics as measured by several swallowing outcomes.

9.3 Limitations and Future Research

As both studies in this programme of research utilised a wide range of swallowing assessments in this heterogeneous population, there are several methodological limitations to acknowledge. Firstly, the EAT-10 screening questionnaire was utilised for participant inclusion; subsequent concerns have been raised regarding the psychometric properties of this tool (Cordier et al.,

2017). As this was one of the key identifiers of dysphagia in conjunction with reports from the referring professional, this could explain the relatively mild differences in this group's swallowing biomechanics measured by instrumental assessments making functional improvement more difficult to measure. As noted by Plowman and colleagues (2019), the inclusion of participants with near-normal swallowing safety also limited the ability to measure the impact of treatment. Implementation of a higher EAT-10 cut off point may be beneficial in future studies to improve sensitivity and specificity, maximise enrolment of participants with impaired swallowing and avoid potential ceiling effects (Schlickewei et al., 2020). The SWAL-QoL results may also be limited by the reliability of patient responses. The observed treatment effect may reflect a participation effect consistent with other studies where improvements were reported in both treatment and placebo groups (Reyes et al., 2015; Troche et al., 2010). Future studies could utilise disease specific screening such as the HD Dysphagia Scale (Heemskerk et al., 2014), a self-reported questionnaire to measure the presence and severity of dysphagia to identify patients with swallowing dysfunction. In addition, swallowing function quantified and compared to normative data during screening with the TWST and TOMASS as part of the inclusion criteria could identify and include patients with more severe dysphagia.

Conflicting results have raised questions as to which parameters of swallowing biomechanics are more susceptible to change following this treatment. Additionally, these conflicting results may highlight shortfalls with the methods selected, with inadequate sensitivity to change or elements of systematic measurement error. This issue of inconsistency across swallowing outcomes has been highlighted in other areas such as head and neck cancer treatment. Nund and colleagues, (2019) suggested that the vast number of methods available to measure swallowing results in a lack of consistency in measurement of swallowing outcomes. There is a need to develop international consensus for a set of core swallowing outcome measures

sensitive enough to capture treatment effects with good reliability and validity (Nund et al., 2019).

The treatment study compiled group data using two different US systems which varied in terms of image quality. The test-retest reliability study only evaluated one of these devices which limited transferability between studies. Although previous studies reported technical difficulties with the Clarius^{TM} US devices (Hammond, 2019; Winiker, 2019), there were no significant technical issues in this study. Difficulties with visualisation of VFSS videos and maintaining consistent positioning during data collection was challenging for both the participants and the investigators. The use of a radio-opaque coin provided some visual indication of involuntary head rotation or tilt out of optimal position in these studies. This could reduce the reliability of measurements and increase the possibility of measurement error. Future studies may benefit from a three-dimensional radio-opaque ball to improve calibration reliability during VFSS data extraction (Kahrilas et al., 1993). As previously mentioned, the instrumental measures of swallowing biomechanics included several steps of data acquisition and extraction, which provided more opportunity for measurement error and rater error. The poor inter-rater reliability of VFSS outcomes may limit the capacity to observe change in this cohort. Although both raters followed the identical instructions, there was room for rater/rating bias which may not have been present in Leonard and Kendall's work. Further investigation is required to evaluate the sensitivity of alternative methods of VFSS measurement described across the literature (Baijens et al., 2013aSteele, 2020 #1104; Kim & McCullough, 2008; Leonard & McKenzie, 2006; Logemann et al., 2000; Molfenter & Steele, 2014; Sia et al., 2012) in this patient population. In addition, the use of semi-automatic computational software may increase reliability of measures (Leonard, 2019a; Schwertner et al., 2016). Further group data would be beneficial to fully understand neural changes in response to skill-based swallowing

training, as a valuable and interesting adjunct to swallowing outcome measures in a larger patient cohort.

This study was limited by the lack of objective classification of participant genotype and phenotype. Information such as individual CAG repeat score and symptom trajectory from the UHDRS total motor score were unavailable for collection in these studies. This key information could be used to quantify disease progression, dependence for ADLs and pathological burden using the standardised age-CAG product (Ross et al., 2014), disease burden score (Penney Jr et al., 1997) and UHDRS total functional capacity score (Huntington's Study Group; Kremer, 1996). This information should be included in future studies to allow for more detailed interpretation of dysphagic characteristics associated with disease.

It is acknowledged that this study was limited by the small sample size which can restrict the overall power of the analysis. This small number could also increase the possibility of Type I or Type II errors using multiple statistical tests affecting the interpretation of meaningful results. However, this is considered proof of concept research for intervention in this patient group and will provide valuable feasibility information and data for power calculation to inform subsequent research trials. The feasibility of a treatment study with enough power to detect change in HD is challenging (Frost et al., 2017). Difficulties with recruitment of HD participants for rehabilitation research has been acknowledged in many studies, where several sites and research groups have been utilised for maximum participant inclusion (Busse et al., 2017). The sample size of 12 in our treatment study is comparable to many rehabilitation studies from the HD corticospinal literature (Bohlen et al., 2013; Frese et al., 2017; Quinn et al., 2020). Due to the small sample size and heterogeneity of participants, further evaluation of these swallowing outcomes measures with specified patient groups at various disease stages

would be beneficial. This feasibility study did not include a matched healthy control group; however, the selected swallowing measures all have normative data available. HD participants included in both studies produced high residual variance for several swallowing outcome measures. Interpretation of the reliability of these measures was difficult in a small sample as this between-participant variance contributed to the ICC results. The assumptions for statistical analyses were not met for some of the reliability measures, therefore results should be interpreted with caution. Other studies have highlighted factors such as high variability of data, inconsistent patterns of behaviour over time and complexity of the experimental design which resulted in less consistent conclusions (Harrington & Velicer, 2015). Overall, future research should include participants at various disease stages with brain imaging to understand how dysphagia intervention may enhance neural plasticity (Andrews et al., 2015). A matched control group would be optimal in the next phase of clinical research to identify any treatment effects (Plowman et al., 2019), although the number required may be very difficult to recruit in this rare genetic disease.

Perhaps the number of sessions over two weeks was insufficient to elicit significant changes in swallowing biomechanics in HD. Other studies have reported significant treatment effects after two weeks of skill-based swallowing rehabilitation (Athukorala et al., 2014) and sensorimotor rehabilitation in other neurodegenerative diseases (Burciu et al., 2013). In addition less intensive systematic rehabilitation protocols have demonstrated beneficial effects, for instance three sessions per weeks over nine months (Bartlett et al., 2019; Cruickshank et al., 2015; Reyes et al., 2020); however, as this skill-based dysphagia intervention is based in the principles of motor learning, the high intensity, repetitive practice is likely to be necessary in order to influence neural re-organisation and modulation of swallowing (Kleim & Jones, 2008; Krakauer, 2006; Zimmerman et al., 2020). Although the optimal dose of swallowing

rehabilitation has yet to be identified across the literature, most MDT programmes demonstrating significant changes in functional outcomes in HD involved a minimum of three weeks intensive rehabilitation (Ciancarelli et al., 2013; Mirek et al., 2018; Piira et al., 2014; Reyes et al., 2015; Zinzi et al., 2007). Future research should aim to replicate this skill-based dysphagia rehabilitation with a larger sample size over at least three weeks to investigate any treatment effects. It is possible that the optimum dose of treatment in HD is not feasible for individuals or fiscally viable for health care systems, therefore post-rehabilitation follow-up is required to provide evidence of any maintenance effects.

9.4 Conclusion

Swallowing dysfunction in neurodegenerative disease contributes to the leading cause of death and compensatory approaches such as diet modification and non-oral feeding are frequently prescribed despite poor evidence and adherence (Espinosa-Val et al., 2020). Rehabilitative approaches for swallowing continue to be a largely unexplored area, particularly in HD. These methodological and treatment studies present the first attempt to fill substantial gaps in the literature regarding reliable measurement of swallowing characteristics and swallowing rehabilitation approaches for individuals with HD. This research has reported the reliability of standardised swallowing outcome measures to aid selection and interpretation for future intervention studies. Of note, reliability of dynamic swallowing biomechanics was affected by the complex, multi-step measurement techniques as well as the highly variable swallowing characteristics within and across individuals with HD.

This exploratory treatment study did not provide evidence that this skill-based training altered swallowing biomechanics in HD. It did, however, provide sufficient evidence to support the feasibility and acceptability of intensive swallowing rehabilitation using sEMG biofeedback. This novel training protocol demonstrated behavioural and self-reported improvements in QoL

with no evidence of detrimental effects or functional deterioration. Due to the diverse patient cohort, these findings are not clearly generalised to allow clinicians to identify which HD patients may benefit from swallowing rehabilitation. Perhaps swallowing biomechanics in HD are less amenable to change through rehabilitation. This research, however, provides reason enough to further explore treatment approaches with altered protocols and larger groups to address the current limitations and allow for generalisation of findings.

These studies lay the foundation for future research investigating swallowing rehabilitation in neurodegenerative conditions. Clinicians and researchers are encouraged to use this information to objectively measure and monitor dysphagia characteristics in patients with HD. Replication of this and other skill-based treatment approaches with a larger sample size will further develop our understanding of specific dysphagia characteristics associated with HD stages, and investigate the long-term treatment effect of skill-based training on HD dysphagia progression.

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Appendix A – Systematic Review

Journal of Huntington's Disease 9 (2020) 1–12
DOI 10.3233/JHD-190384
IOS Press

Review

A Systematic Review of Rehabilitation for Corticobulbar Symptoms in Adults with Huntington's Disease

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Abstract.
Background: Corticobulbar symptoms have been reported in all stages of Huntington's disease (HD); aspiration pneumonia associated with swallowing impairment has been identified as the most common cause of death. Whilst recent research has described positive effects of corticobulbar rehabilitation in other neurodegenerative conditions, it is unclear if this is similarly effective in HD. Preliminary evidence in corticospinal rehabilitation has revealed physical therapy and exercise could be beneficial for individuals with HD.
Objective: This systematic review will explore the literature relative to rehabilitation of corticobulbar symptoms in adults with HD.
Methods: Two investigators independently searched relevant electronic databases for literature related to corticobulbar rehabilitation in HD, published in English until October 2019. Included studies were critically appraised using the Oxford Centre for Evidence-based Medicine Levels of Evidence, Cochrane Risk of Bias Tool and Scottish Intercollegiate Guidelines Network checklists. Study outcomes included measurements of function, quality of life or neuromuscular physiology.
Results: Seventy-seven publications were screened with eight studies meeting the inclusion criteria – two randomised control trials and six intervention studies. Validated and objective outcome measures of corticobulbar symptoms were infrequently used. There was a high risk of bias identified in 7/8 studies. The data suggested positive clinical outcomes, no adverse effects and no deterioration observed across longitudinal studies.
Conclusions: This systematic review documented a lack of high-quality evidence to support the use of rehabilitation to treat corticobulbar symptoms in HD. However, the suggestion of potential positive effects based on available, albeit limited, studies provides justification for further research in this area.

Keywords: Huntington's disease, bulbar, dysphagia, swallowing, speech, dysarthria, treatment, rehabilitation

INTRODUCTION

Despite the recent progression in clinical trials and pharmaceutical therapies to slow or alter the progression of Huntington's disease (HD), there are currently no effective medical treatments [1, 2]. It is therefore important to maximise proactive behavioural

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interventions to maintain function and improve quality of life. The role of rehabilitation to treat neurodegenerative diseases is a concept with emerging evidence in several conditions, including HD [3–5].

The majority of individuals with HD will develop corticobulbar symptoms [6]. These often present as noticeable changes in speech (dysarthria) and swallowing (dysphagia). Whilst these symptoms may be primarily related to progressive cortical neurodegeneration, evidence also highlights that commonly prescribed anti-choreic medications have side effects which include dysphagia, xerostomia (dry mouth), dysarthria and drowsiness [7–9]. Corticobulbar impairments such as dysphagia and dysarthria are highly correlated with decreased quality of life, independence and increased care giver burden [10–14]. The impact of cognitive impairment and changes in mood, combined with corticobulbar symptoms affect the ability to communicate successfully and participate in meaningful social interactions [15]. Dysphagic and dysarthric symptoms will be the key focus of this review.

Oropharyngeal dysphagia and dysarthria have been widely reported in all stages of HD [15–21]. Whilst these corticobulbar symptoms are highly variable between individuals, there are identified correlations between the severity of dysphagia, dysarthria and disease progression [6, 22]. In HD, all phases of swallowing can be impaired, impacted by choreic movements, cognitive impairment and behavioural changes [6]. Abnormal swallowing physiology in HD compromises swallowing safety with aspiration pneumonia reported as the leading cause of death in this condition [23, 24]. In addition, motor speech changes associated with HD can fall into several dysarthria categories; however, features of hyperkinetic dysarthria are most commonly described in the literature [25, 26]. Speech in HD is typically characterised by rapid involuntary movements of respiration, phonation, and articulation impacting on speech production, prosody and resonance [15, 21, 27]. Many people are unable to communicate effectively at the end stages of the disease.

In recent years, there has been an increase in studies evaluating corticospinal rehabilitation and exercise for individuals with HD [28–31]. Physical therapy and exercise interventions were reportedly well tolerated, resulting in measurable improvement in function during daily activities, cognition and self-reported quality of life [29, 30, 32]. Bilney et al. [5] also reported some functional improvements in gait and balance following multidisciplinary interventions in individuals with HD. European Huntington's Disease Network Physiotherapy Guidelines have recommended targeted behavioural treatment for people in early to mid-stage HD to improve or maintain functional ability [33]. These guidelines reflect best available evidence and suggest no detrimental effects of intensive behavioural interventions.

This emerging evidence highlights the importance of behavioural interventions and exercise combined with pharmaceutical therapies in the long-term management of HD. An active rehabilitative approach to target corticospinal symptoms has been described as a crucial part of individual HD management [8, 30, 34]; however, the efficacy of rehabilitation targeting corticobulbar symptoms has not yet been reviewed. Compensatory strategies are most commonly applied to manage dysarthria and dysphagia as active rehabilitation has historically been assumed to be detrimental in neurodegenerative populations [3]. Importantly, a careful review of the literature in amyotrophic lateral sclerosis reveals insufficient evidence to suggest that moderate-intensity rehabilitative approaches are contraindicated in this neurodegenerative population [3]. Thus, the present review was conducted to explore the literature relative to rehabilitation of corticobulbar symptoms in adults with HD. This then forms the foundation for future research aimed to maintain or improve corticobulbar function in HD.

MATERIALS AND METHODS

The methodology for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42017064156) and aligned with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two investigators independently searched electronic databases for published literature in English until October 2019 using Medline-Ovid, Embase-Ovid, CINAHL, Web of Science (science and social science citation index), Science Direct, Scopus, Pubmed, The Cochrane Library (Cochrane Database of Systematic Reviews), clinical trial registers and best practice guidelines. The search strategy firstly identified the appropriate MeSH terms using the 'map to MeSH term' function in the Ovid version on Medline. This process was then repeated for each bibliographic database and relevant papers were screened for

additional MeSH terms. These key words were then included in the subsequent literature searches. Key words used were: Huntington, Huntington's disease, Huntington's chorea, dysphagia, deglutition, bulbar, swallowing, speech, dysarthria, motor speech, articulation disorders, treatment and rehabilitation. All selected studies were manually cross-referenced to ensure no relevant literature was missed. The search was repeated prior to the final analysis. Abstracts, and then full articles, were reviewed collaboratively to compile a final list for review.

Studies met the inclusion criteria if they evaluated intervention with adults with manifest Huntington's Disease, who had reported Shoulson & Fahn Staging 1–5, or presence of $\geq$36 CAG trinucleotide expansion repeats confirmed via genetic testing [35]. Articles with Juvenile HD (JHD) participants were not included as the significantly higher CAG repeats reported in JHD often result in more severe early cognitive and behavioural impairment, as well as faster disease progressions. Articles were included if they aimed to result in long term changes in the underlying neuromuscular substrates that present as corticobulbar symptoms in HD. This included interventions targeting the corticobulbar pathway. Specifically, direct innervation to cranial nerves III, IV, V, VI, VII, IX, X, XII or the muscles of the face, tongue, jaw, pharynx, head and neck. Sensory interventions that aimed to rehabilitate the corticobulbar pathway were also included. Literature excluded from this review were any interventions that focussed solely on compensatory strategies in isolation, such as modified diets, utensil modification, increased supervision.

Data extracted from the studies were grouped, compared and summarised using structured narrative (descriptive) analyses including specific population (e.g. stage of Huntington's disease), intervention content, intervention effects and outcome measures where possible. Included studies were critically analysed using the Scottish Intercollegiate Guidelines Network (SIGN) Algorithm and Critical Appraisal Checklists [36, 37]. Levels of evidence were rated according to Oxford Centre for Evidence-based Medicine Levels of Evidence [38] and risk of bias was judged using the Cochrane Risk of Bias Tool [39, 40].

RESULTS

In total 888 publications were identified. As detailed in the PRISMA flowchart (Fig. 1), 77 full text articles were reviewed, 19 studies were excluded as they described compensatory management only. Of the remaining 58, only eight studies matched the inclusion criteria: two randomised control trials (RCTs) and six intervention studies evaluated rehabilitative approaches to improve corticobulbar symptoms. It is acknowledged that one of the RCTs evaluated rehabilitation of olfactory (CN I) function, which is not specifically included in the corticobulbar pathways [41]. This study was included given potential impact of olfaction on other corticobulbar symptoms in HD. See Table 1 for a summary of included studies. Using the SIGN Algorithm [36], only two studies were rated as appropriate to assess quality of evidence using the SIGN Critical Appraisal Checklists (see the Supplementary Material) [37]. The remaining studies were critically analysed using the Cochrane Risk of Bias Tool, and descriptively reviewed below. Quantitative data synthesis was not possible as the low yield of articles used varied outcome measures and therefore were not sufficiently homogenous.

Descriptive analysis of key study features

Study design

Table 1 outlines the study designs that were used to evaluate the effectiveness of rehabilitation in individuals with HD. Two studies were RCTs and adopted control groups who received sham treatment [41, 42]. The remaining five studies were within-subject intervention case series/cohort studies [13, 43–46]. Participants were assessed pre- and post-intervention. One of these inpatient study designs then used a non-standardised questionnaire mailed to participants who had completed the first rehabilitative study [13].

Participants

Treatment groups ranged from five [46] to 40 [43] participants who completed corticobulbar interventions. All studies included individuals at varying stages of the disease which limits comparison of rehabilitation approaches. The Unified Huntington's Disease Rating Scale (UHDRS) was used in two studies to characterise the stage and severity of the disease [42, 46]. Subcategories of this scale were also used as outcome measures in two other studies [44, 45]. One study included only individuals with mild HD (Stage 1 or 2 according to the UHDRS) [46]. The majority of studies included participants with mild-moderately advanced HD [13, 43–45], whilst Leng

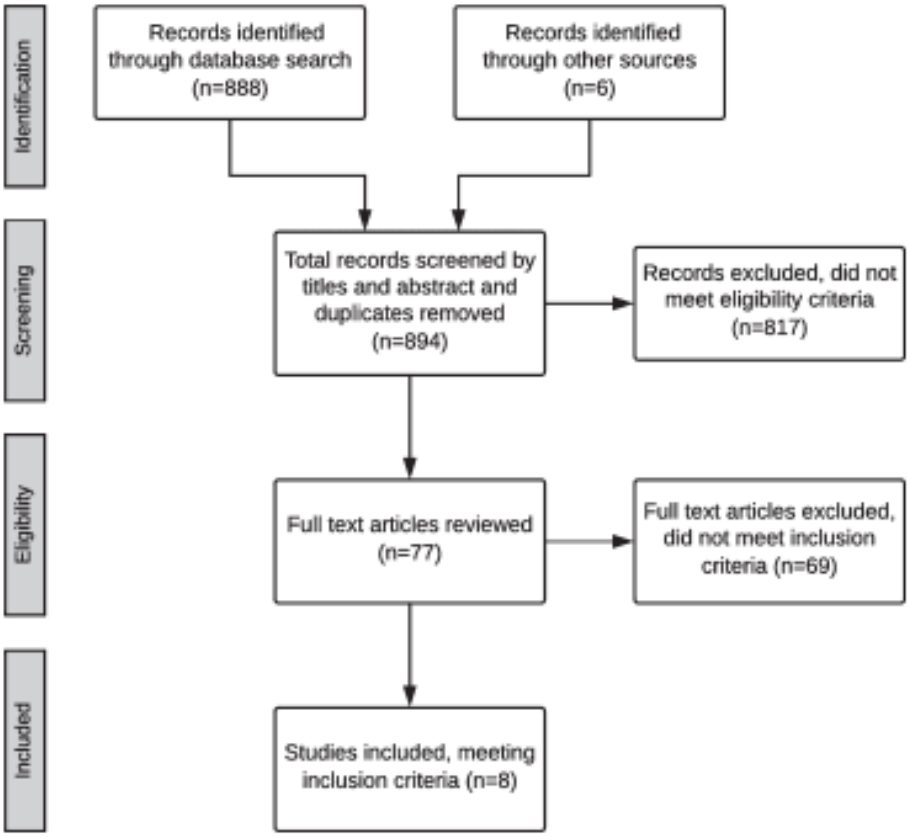

Fig. 1. PRISMA Flowchart for identifying studies for systematic review.

et al. [41] included only late-stage (stage 5) HD in their recruitment.

Setting of therapy

Intervention took place in a variety of settings and with different service delivery models. Four studies took place in inpatient facilities and included MDT rehabilitation [13, 43–45], one in a specialist residential home [41], two were home-based programmes of daily exercises [42, 46] and one was in an unspecified outpatient clinic [47]. All studies reported good adherence to therapy programmes and participation in intervention across settings; however, no systematic measurements of adherence were reported.

Intervention

Interventions to maintain or improve speech and swallowing were intensive; six studies evaluated daily intervention [13, 43–46], one completed sessions twice per week [41], and one stated that 11/12 patients were "intensively treated" but did not specify what this consisted of [page 59, 47]. Where specified, the duration of intervention ranged from three weeks [13, 43–45] to four months [42]. Giddens et al. [46] reported that oral motor labial and lingual resistance training, respiratory (glottal adduction) and phonatory exercises were completed twice daily at home, a minimum of four times per week for 30 days. The number of participants that fully adhered to the long-term exercise program was not reported. Similarly, Reyes et al. [42] evaluated inspiratory and expiratory muscle training using a home programme of six training sessions per week for four months. The training group received increased resistance to respiratory pressures over the course of treatment, whilst the control group received a sham protocol with the same device. There were no adverse effects of intensive training and all participants adhered to the protocol, but it is not reported if the adherence to the home programme was specifically measured [42].

Four studies evaluated interventions to maintain or improve speech and swallowing function as part of an intensive inpatient MDT approach [13, 43–45]. Two of these articles specified the intensity of their

Table 1
Summary of 8 studies included in this systematic review of corticobulbar rehabilitation in adults with Huntington's disease

Author	Participants	Study Design & Level of Evidence	Treatment	Outcome Measures	Results/conclusions
Leopold & Kagel [47]	N = 12, 11 moderate HD, 1 mild-moderate HD.	Intervention case series (2b)	Modified Valsalva maneuver, modification of diet, utensils, and posture. Individualising swallowing sequence.	Neurological examination, pulmonary function testing, oesophageal manometry, laryngoscopy and videofluoroscopic swallowing study. Diet modification level.	Improved bolus prep and transfer, pre-mature swallow, pharyngeal stasis, nasopharyngeal reflux and aspiration. 8/11 participants returned to a normal diet. 3/11 minimally restricted diet. Maintained for 3 years.
Leng et al. [41]	N = 12, mid-late HD in a specialised residential unit. (2 withdrawn with medical complications)	Randomised controlled pilot study. Two group design. (2b)	1:1 Multisensory stimulation targeting visual, tactile, auditory, olfactory input (MSE, treatment) versus relaxation (control group). 30mins twice weekly for four weeks.	Rehabilitation Evaluation and Behaviour and Mood Disturbance rating scales. Interact observation assessments (pre, during and post-therapy sessions). Physiological measures e.g. respiration and involuntary movements.	Significant difference in mood during MSE sessions, and stimulation level over time. Effects did not generalise between sessions. No other significant differences.
Zinzi et al. [43]	N = 40, mild-moderate HD (25 completed study)	Pilot study (2b)	Individual and group intervention (PT, OT & SLT) in an inpatient rehabilitation facility. 3 week block of intensive treatment. Treatment block could be repeated 3 times a year. 8 hours of intervention per day 5 times a week, 4 hours for 1 day, 1 day free.	Zung Depression Scale, Mini-Mental State Examination (MMSE), Barthel Index, Tinetti Scale, Physical Performance Test (PPT).	Each 3 week block of treatment resulted in highly significant ($p > 0.001$) improvements in motor performance and activities of daily living. No carry-over effect from one admission to the next but no motor decline was detected over two years. Dysarthria and dysphagia specific measurement in Barthel Index and PPT were not stated.

(*Continued*)

Table 1
(*Continued*)

Author	Participants	Study Design & Level of Evidence	Treatment	Outcome Measures	Results/conclusions
Zinzi et al. [13]	N = 40 who had completed at least one block of intensive treatment described above. Average 8.6months follow up.	Retrospective case series, intervention (2b)	A written questionnaire mailed to participants and their carers.	Descriptive and inferential statistics were used. Thematic analyses were also conducted on written texts.	Improvements were reported in speech, swallowing, and several psychosocial aspects: mood, apathy, familiar and social relationships (binomial test, $p < 0.05$). Improvements in gait, balance, motor control, and fall reduction were also described. Duration of benefits estimated to last 1–3 months by 71% of informants with no carry over to the next admission.
Giddens et al. [46]	Case series: *N* = 14 13 early HD, 1 late HD Pilot study: *N* = 7, early HD (5 completed study)	Case study & Pilot study (4)	Home-based oral motor, phonatory and respiratory exercises. Twice daily for 30 days	Cranial nerve examination Speech diadochokinetic rates, maximum phonation.	2/5 patients reported 'elimination' of dysphagia. Improved or maintained cranial nerve function and phonation time.
Piira et al. [44]	N = 37, early-mid stage HD (31 completed study)	Intervention study (2b)	Daily 1:1 or group therapy (PT, OT & SLT). Exercises focused on improving muscle strength, maintaining function, included unspecified swallowing/speech exercises at least 3 times per week and diet modification at rehabilitation centre. Family/caregiver education training. 3 week block of intensive treatment. Treatment block could be repeated 3 times a year.	MMSE and Unified HD Rating Scale. Motor Function: 6min walking test, TUG, 10m test, BERG balance scale. ADLs: Barthel Index Cognitive function, Hospital Depression & Anxiety Scale, Quality of Life SF 12 questionnaire.	Significant improvements in gait function, balance, quality of life, anxiety and depression, BMI. ADLs and functional ratings remained stable. Significant decline in only one cognitive measure (SDMT). No other decline. Dysarthria and dysphagia specific measurement in Barthel Index were not stated.

Piira et al. [45]	N = 6 from, 10 early-mid stage HD who completed previous study above [44].	Retrospective intervention study (2b)	Daily MDT intervention as described above [44]. 6 admissions of 3 weeks over a 2 year period.	Same outcome measures as above [44].	No significant decline in gait and balance from 2 year baseline. Some improvement in BMI, QoL, anxiety and depression, did not reach significance. No significant decline in cognition. ADL stable. 4/6 improved motor function. Dysarthria and dysphagia specific measurement in Barthel Index were not stated.
Reyes et al. [42]	N = 18, moderate HD. Randomised to control group ($n = 9$) and training group ($n = 9$).	Randomised Control Trial (1b)	Home-based inspiratory and expiratory muscle training (5 sets of 5 repetitions) 6 times a week for 4 months. Control group: fixed resistance. Training group: progressively increased resistance.	Spirometry indices, maximum inspiratory and expiratory pressure, 6min walk test, dyspnoea, water swallow test, SWAL-QoL.	Intervention group improved in respiratory outcome measures, time per swallow, SWAL-QoL. Small positive effect on respiratory outcomes for control group.

intervention which focused on physical exercise, social activities, and family/caregiver education teaching sessions [44, 45]. SLT intervention was reported, but specific dysarthria and dysphagia exercises were not described in any of the MDT studies, thus inhibiting replicability. Zinzi et al. [43] included non-specified speech therapy where patients were "taught strategies for swallowing" [page 40, 42] amongst other MDT intervention. This study also completed respiratory exercises using visual and tactile feedback during joint sessions with the physiotherapist and SLT [43].

Leopold et al. [47] provided a description of their dysphagia intervention which included a modified Valsalva manoeuvre (forced exhalation against a pinched nose) alongside compensatory strategies (diet modification, adaptive utensils, optimum positioning). Patients were taught the 'chew-swallow-cough-swallow sequence' technique. An unspecified number of the twelve participants with severe dysphagia required non-oral feeding to maintain nutrition and hydration via nasogastric tube until the "compensatory techniques could be instituted and a pureed diet could be safely tolerated" [page 59, 47]. The authors stated that "more severely demented patients required more sessions" [page 60, 47] and greater ongoing supervision post-therapy to target more severe cognitive and motor sequencing deficits; however, this additional therapy was not clearly defined. The duration of the intervention was not stated, and the results were not statistically analysed.

Leng et al. [41] did not focus on dysarthria or dysphagia intervention. Instead, this study measured the effect of multisensory environmental stimulation (MSE) compared to passive relaxation therapy. The standardised MSE intervention was designed for visual, tactile, auditory and olfactory innervation. The authors described the specific intervention sufficiently to allow for replication.

Outcome measures

All intensive MDT intervention studies included broad outcome measures of motor performance (including walking, gait, and balance), ratings of ability to perform activities of daily living (ADL), cognitive measures (typically the Mini-Mental State Examination and UHDRS) and quality of life measures [13, 43–45]. No instrumental or objective measures of speech or swallowing were reported in these studies; however, the Barthel Index (a measure of ADL) includes questions about feeding

independence and diet modification. Piira et al. [45] used these baseline measures to report no functional decline in cognition, ADL, gait or balance in participants who continued the rehabilitation programme for another year after initial admission. Zinzi et al. [43] also used the Physical Performance Test (PPT) to measure the functional speed and accuracy of specific tasks. This standardized test included a measure of functional eating. The authors reported significant positive treatment effects on motor and functional performance as measured by the PPT and Tinetti Scale. This improvement was not retained between inpatient admissions. The authors highlighted an overall lack of decline in other cognitive and functional measures such as the Barthel Index over the two year follow up period [43].

Many studies included subjective or non-standardised measures of corticobulbar symptoms. Giddens et al. [46] used an unspecified swallowing screening with no instrumental assessment or functional outcome measures. They reported significant improvements post-therapy on subjective oral motor ratings and diadochokinetic ratings. Two of the six participants self-reported an 'elimination' of their swallowing impairment post-therapy, but there were no objective measures of this. Conversely, Leopold et al. [47] described several objective assessments of swallowing including videofluoroscopic swallowing studies, oesophageal manometry, pulmonary function testing, mealtime observation and neurological examination. All participants demonstrated clinical abnormalities of swallowing, speech and voluntary coughing. Each participant was rated on a non-standardised dysphagia severity scale (0 – 5) using instrumental assessment findings. Videofluoroscopic assessment was the only outcome measure repeated post-therapy and was reported descriptively by the authors. No objective timing or displacement measures were used to analyse the videofluoroscopic studies. The study reported that all participants improved and 73% ($n = 8$) returned to normal diet; the remaining three were advised to have minimal diet restrictions. These improvements were maintained for up to 3 years post-treatment. This was inferred as none of the participants required supplementary or additional non-oral nutrition; however, no objective follow up assessments were reported.

Reyes et al. [42] used spirometry measures of inspiratory and expiratory pressures pre- and post-treatment. A non-standardised version of the timed water swallowing test was used to measure functional swallowing ability with thin fluids. Participants were instructed to drink 50mls of water three times in each assessment session. The standardised Timed Water Swallow Test is 150mls of water consumed "as fast as is comfortably possible" [48]. Time per swallow, swallowing capacity and volume improved at two months and four months of training. Swallowing related quality of life (SWAL-QoL) improved slightly after four months of training. This study did not include any objective or instrumental measures of swallowing biomechanics. The treatment group had a moderate training effect on maximum inspiratory and expiratory pressures after four months of training. A small effect was also reported for the control group. Improvements were also noted in spirometry measures compared to the control group; however, these differences were not statistically significant. Non-significant improvements were also reported across swallowing measures, including the adapted timed water swallowing test. No studies included secondary information regarding pulmonary status, rate of chest infection or aspiration pneumonia.

As previously discussed, Leng et al. [41] focused on a multisensory environment to evaluate the effects of visual, tactile, auditory and olfactory stimulation. This study did not include any direct measurements of corticobulbar function, instead the primary measures were of mood and behaviour using the Rehabilitation Evaluation and Behaviour and Mood Disturbance rating scales. Physiological measures including heart rate, respiratory flow and involuntary movements (using the dyskinesia section of the St. Hans Rating Scale) were collected throughout the 12 week observation period. The reliability and validity of these outcome measures were not discussed, particularly in relation to assessment of people with HD. The researchers found an immediate effect of intervention on mood during MSE sessions, and stimulation level over time compared to the control group, but these effects did not generalise between sessions. There were no other significant differences between groups in respect to involuntary movements or other measures. Although speech and swallowing symptoms were not included in this RCT, this study evaluated a rehabilitation which partially targeted olfactory (CN I) function. This study was considered relevant to include to reflect its impact on other corticobulbar symptoms in HD.

Risk of bias

A summary of the Cochrane Risk of Bias Tool completed for each study is provided in Table 2. Low risk

Table 2
Summary of Cochrane Risk of Bias Tool evaluation. H, high risk of bias, L, low risk of bias, U/C, unclear risk of bias

	Sequence generation	Allocation concealment	Blinding (pts/researchers)	Outcome ax blinding	Incomplete data	Selective reporting	Other bias
Leopold & Kagel [47]	N/A	N/A	N/A	H	H	H	H
Leng et al. [41]	L	L	H	H	L	L	U/C
Zinzi et al. [43]	N/A	N/A	N/A	U/C	H	L	U/C
Zinzi et al. [13]	N/A	N/A	N/A	H	L	H	H
Giddens et al. [46]	N/A	N/A	N/A	H	H	H	H
Piira et al. [44]	N/A	N/A	N/A	H	H	L	U/C
Piira et al. [45]	N/A	N/A	N/A	H	H	L	U/C
Reyes et al. [42]	L	L	U/C	U/C	L	L	U/C

of attrition bias was identified in 3/8 of studies [13, 41, 42], where complete outcome data were reported. Additionally, there was low risk of bias in selective reporting in 5/8 of studies [41–45]. The method of data collection adopted by Zinzi et al. [13] was judged to have a high risk of bias. Their non-standardised questionnaire was mailed to participants on average 8.6 months post-intervention. This questionnaire asked about their inpatient rehabilitation and care experience; 91.9% ($n = 34$) of respondents were caregivers and 8.1% ($n = 3$) respondents were patients who had completed the inpatient intervention. This method of data collection may have introduced a recruitment bias and selective reporting as people generally reported positive improvements on this subjective questionnaire.

Giddens et al. [46] excluded participants with more severe cognitive or motor impairments creating a risk of selection bias. One participant with late (stage 4) HD was withdrawn from the study as she subjectively perceived increased muscle weakness with the exercise program, however, there were no clinical measures of this. Two participants changed their drug regimens during treatment which created an additional variable. Whilst Leopold et al. [47]'s landmark study published in 1985 is frequently referenced to describe dysphagia in HD, the adopted study design is vulnerable to several identified biases. Blinding of raters was not possible, outcome measures were not validated, or consistently repeated post-therapy. In addition, data analysis of quantitative outcome measures was not conducted.

Both RCTs included in this review were deemed low risk of bias in several domains [41, 42]. The authors provided a detailed protocol for randomisation and intervention, including baseline and follow up periods to measure any treatment effect. These study designs were replicable and reduced risk of bias, despite the small sample size. Leng et al. [41] used two investigators to facilitate and score the sessions, with good inter-rater reliability reported; however, with this design blinding was not possible. Two participants withdrew from this study due to medical complications which may have increased selection bias, and significant changes in medication were reported for two participants during the study, introducing an additional variable. The other RCT excluded those with moderate-severe corticobulbar symptoms such as lingual chorea and oral weakness which may have introduced a selection bias [42].

DISCUSSION

Historically, SLT management of HD focused on compensation for speech and swallowing impairment with approaches such as diet modification, increased supervision, postural changes, stabilising the mandible, and visual cues [47, 49]. Indeed, within the screened literature, 17 articles did not meet the inclusion criteria as they only described compensatory management of dysphagia and dysarthria. Whilst these strategies may be important to implement as the disease progresses, it may be worth considering the potential for rehabilitation, particularly for treatment of dysphagia and dysarthria.

This systematic review revealed a lack of high-quality evidence to justify the effectiveness of rehabilitation for corticobulbar symptoms in HD. Despite this, the included studies highlighted preliminary evidence of potential benefits of ongoing research regarding rehabilitation for corticobulbar symptoms, such as dysphagia and dysarthria. Importantly, there was no significant deterioration observed across longitudinal studies, which could be clinically significant in this neurodegenerative disease. This conclusion may be taken cautiously given that the full trajectory of disease progression is not known; however, with a study duration of up to three years, it suggests at the very least, a possible short-term

positive impact [13, 43–45, 47]. Further investigation into the effectiveness of specific rehabilitative approaches is warranted as five of the included studies failed to describe which dysarthria or dysphagia interventions were used [13, 43–45, 47]. Of the interventions described in three studies, there was inadequate homogeneity to allow for comparison between rehabilitation methods [41, 42, 46].

In HD, corticobulbar deficits are not isolated to muscle weakness [10, 49]. An alternative approach may be to focus on optimising precision of neuromuscular connections instead of primarily compensatory management. Giddens et al. [46] hypothesised that the significant improvement observed in cranial nerve function following intensive rehabilitation may be attributed to better control and coordination of the muscle groups integral to speech and swallowing. Task specific rehabilitation based on the principles of motor learning may be beneficial in HD management; as these intensive rehabilitative approaches have shown potential to increase neuroplasticity and cortical excitability [50, 51]. Structured rehabilitative programmes which intensively target dysarthria or dysphagia such as Lee Silverman Voice Treatment, expiratory muscle strength training (EMST) and video-assisted swallowing (VAS) therapy have been evaluated in other neurodegenerative diseases. Studies evaluating these rehabilitative approaches have reported benefits following treatment to maintain or improve function in conditions such as amyotrophic lateral sclerosis, multiple sclerosis and Parkinson's disease, [42, 52–55]. As Reyes et al. [42] evaluated the effects of a structured EMST protocol in HD, this small RCT provided preliminary evidence to suggest this muscle strengthening intervention may be beneficial in HD. This justifies further research into task specific skill-based interventions and muscle strengthening approaches with larger sample sizes and instrumental swallowing outcome measures.

This review also highlighted the lack of objective outcome measures used to evaluate therapy. Only one study included the gold standard videofluoroscopic swallowing studies pre- and post-therapy [47]. However, this study did not include standardised timing or displacement measures of swallowing biomechanics. Whilst one study included a swallowing specific quality of life questionnaire [42], the remaining studies included non-standardised or nonspecific measures of corticobulbar function. The omission of valid and reliable outcome measures is problematic for replicability and evaluation of treatment effects. Furthermore, seven of the eight studies were judged to have a high risk of bias identified in at least one category (Table 2). As often seen in the wider literature of this rare neurodegenerative disease, small sample sizes and underpowered studies were identified as limitations in the majority of the studies included in this review (Table 1). Whilst the disease stage or UHDRS scores were described in most studies, other key participant information such as level of cognition, medication regimes, or presence of depression was not specified consistently.

Although the number of studies is limited and the outcome measures lack objectivity, overall the included studies suggested no adverse effects, and at least the possibility of potential benefits of intensive rehabilitation to improve or maintain function. The therapy programmes were reportedly well adhered to, with minimal withdrawal from intervention and no measurable detrimental effects of an intensive approach across several stages of the disease. This is in line with systematic reviews evaluating corticobulbar rehabilitation in other neurological populations [3]. In addition, this echoes the findings of systematic reviews specifically focused on corticospinal rehabilitation and exercise in HD [5, 29, 32, 33]. These reviews highlight the concept that rehabilitative approaches may be beneficial in HD, counter to traditional belief that active rehabilitation may not be effective or tolerated in neurodegenerative diseases [5]. Conversely, there has been a notable increase in interest and literature since 2003 which has provided evidence to support the feasibility and effectiveness of early MDT intervention to maintain or improve function in corticospinal symptoms of HD. This valuable research may inform further development of rehabilitative approaches to target corticobulbar symptoms such as dysarthria and dysphagia.

Conclusion

There was not sufficient evidence to justify rehabilitation of corticobulbar symptoms on HD. The best available research in early to mid-stage HD suggested short-term improvements in motor function and quality of life following intensive functional rehabilitation. However, there was no evidence of detrimental effects from the available studies. The existing evidence was limited by the risk of bias, with a lack of valid and reliable objective tools used. There was, however, sufficient preliminary evidence to justify further research in this area using well designed intervention studies with standardised,

objective outcome measures to evaluate rehabilitative approaches targeting corticobulbar symptoms in individuals with HD.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JHD-190384.

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Appendix B – Test-Retest Study Participant Information Sheet and Consent Form

PARTICIPANT INFORMATION SHEET

Department of Communication Disorders

Email: emma.burnip@pg.canterbury.ac.nz

7th December 2017

Study title: **Reliability of swallowing outcome measures in Huntington's Disease:**

A test-retest pilot study

Lead investigator: Emma Burnip Contact phone number: 03 365 2385

Locality: Canterbury Ethics Committee ref:

You are invited to take part in an assessment study for swallowing difficulties in Huntington's Disease. 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 Emma Burnip, a Speech-Language Therapist and PhD student. I am researching the most reliable assessments to use with people with Huntington's Disease (HD).

- At the moment, there are no options to treat people with swallowing problems caused by HD. We want to find out which are the best assessments to measure swallowing in order to test new interventions to help keep swallowing safer for longer.
- All volunteers will complete three assessment sessions over one week. We will compare measures of swallowing between these sessions to see if there are any differences.
- This will help us to analyse which measurements are most reliable and stable.
- This study is being funded by the University of Canterbury Rose Centre for Stroke Recovery and Research as part of my PhD project.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

- You can join this study if you are 30 years or older and have been diagnosed with Huntington's disease. 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 three assessment sessions over one week (Monday / Wednesday / Friday).
- 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 HD. You will be asked to do a short assessment of thinking skills with the researcher, 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.
- 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.

- All assessment sessions will be carried out at the UC Rose Centre located in at St George's Medical Centre.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

- Some of the assessments have low risks that you should be aware of. 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 and helpful measurements of your swallowing.

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.

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 their health.

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: Emma Burnip, PhD Candidate,

Department of Communication Disorders, University of Canterbury

Telephone number: 03 365 2385 Email: emma.burnip@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:
Telephone number: 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 ETHICSEmail: hdecs@moh.govt.nz

CONSENT FORM

Department of Communication Disorders

Telephone: +64 3 364 2307

Email: emma.burnip@pg.canterbury.ac.nz

7th December 2017

Reliability of swallowing outcome measures in Huntington's Disease:

A test-retest pilot study

If you need an INTERPRETER, please tell us.

Please tick to indicate you consent to the following *(Add or delete as appropriate)*

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.	Yes ☐	No ☐
I have been given sufficient time to consider whether or not to participate in this study.	Yes ☐	No ☐
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.	Yes ☐	No ☐
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.	Yes ☐	No ☐
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.	Yes ☐	No ☐
I consent to the research staff collecting and processing my information, including information about my health.	Yes ☐	No ☐
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.	Yes ☐	No ☐
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.	Yes ☐	No ☐

I understand that there may be risks associated with the assessment in the event of myself or my partner becoming pregnant. I undertake to inform my partner of the risks and to take responsibility for the prevention of pregnancy.	Yes ☐	No ☐
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.	Yes ☐	No ☐
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.	Yes ☐	No ☐
I understand the compensation provisions in case of injury during the study.	Yes ☐	No ☐
I know who to contact if I have any questions about the study in general.	Yes ☐	No ☐
I understand my responsibilities as a study participant.	Yes ☐	No ☐
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:

Appendix C – Treatment Study Participant Information Sheet and Consent Form

PARTICIPANT INFORMATION SHEET

Department of Communication Disorders

Email: emma.burnip@pg.canterbury.ac.nz

6th December 2017

Study title: **Skill-based swallowing training for patients with Huntington's Disease**

Lead investigator: 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 Huntington's Disease. 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 Emma Burnip, a Speech-Language Therapist and PhD student. With a fellow PhD student, Paige Thomas, we are researching a skill-based swallowing therapy.

- At the moment, there are no options to treat people with swallowing problems caused by HD.
- We want to find out whether this new intervention can help swallowing and quality of life in people with HD.
- This intervention uses ideas of skill training and biofeedback to see if people with HD 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 my PhD project.
- 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 30 years or older and have been diagnosed with Huntington's disease. 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 HD. 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:

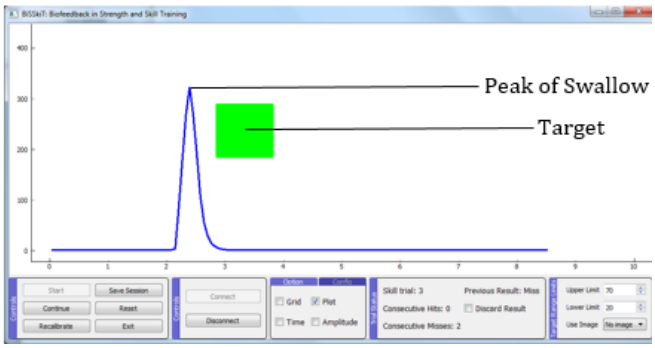
- Have the pressures in your throat measured when you swallow - a small catheter the size of a piece of spaghetti will be inserted into your nose which you will swallow down.
- Have an x-ray study of your swallowing.

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 are 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: Emma Burnip, PhD Candidate,

Department of Communication Disorders, University of Canterbury

Telephone number: 03 369 2385 Email: emma.burnip@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:

Telephone number: 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 3 364 2307

Email: emma.burnip@pg.canterbury.ac.nz

6th December 2017

Skill-based swallowing training for patients with Huntington's Disease

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If you need an INTERPRETER, please tell us.

Please tick to indicate you consent to the following *(Add or delete as appropriate)*

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet.	Yes ☐	No ☐
I have been given sufficient time to consider whether or not to participate in this study.	Yes ☐	No ☐
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.	Yes ☐	No ☐
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.	Yes ☐	No ☐
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.	Yes ☐	No ☐
I consent to the research staff collecting and processing my information, including information about my health.	Yes ☐	No ☐
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.	Yes ☐	No ☐
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.	Yes ☐	No ☐

I understand that there may be risks associated with the assessment in the event of myself or my partner becoming pregnant. I undertake to inform my partner of the risks and to take responsibility for the prevention of pregnancy.	Yes ☐	No ☐
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.	Yes ☐	No ☐
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.	Yes ☐	No ☐
I understand the compensation provisions in case of injury during the study.	Yes ☐	No ☐
I know who to contact if I have any questions about the study in general.	Yes ☐	No ☐
I understand my responsibilities as a study participant.	Yes ☐	No ☐
I wish to receive a summary of the results from the study. If yes to the above- email: _____	Yes ☐	No ☐

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:

Appendix D – Capacity to Consent Form for Test-Retest and Treatment Studies

Swallowing Rehabilitation Clinics

Capacity to Consent Form

Date:

PATIENT DETAILS:

Surname: **First Names:**

Date of Birth: **NHI number:**

Contact Phone: **Sex: M / F**

Address:

GP DETAILS:

Name: **Contact Phone:**

Address:

Information requested:

Please provide an indication as to whether the above patient has the capacity to provide informed consent for a research study.

Requirements:

- **To be able to read and understand the information sheet and consent form.**
- **To be able to answer questions about their swallowing and general health.**
- **To be able to understand and follow instructions about swallowing tasks as part of assessment and training.**

Please tick the appropriate option below:

In my opinion, the above patient DOES have capacity to provide informed consent ☐

In my opinion, the above patient DOES NOT have capacity to provide informed consent ☐

Signature:

Name :

Position:

Contact Number:

Date:

Appendix E – Treatment Study Descriptives: Mean and Standard Deviation of Results

Figure E.1

Bar Graph Representing the Means and Standard Deviation (SD) of Swallowing Quality of Life (SWAL-QoL) Questionnaire Descriptive Data

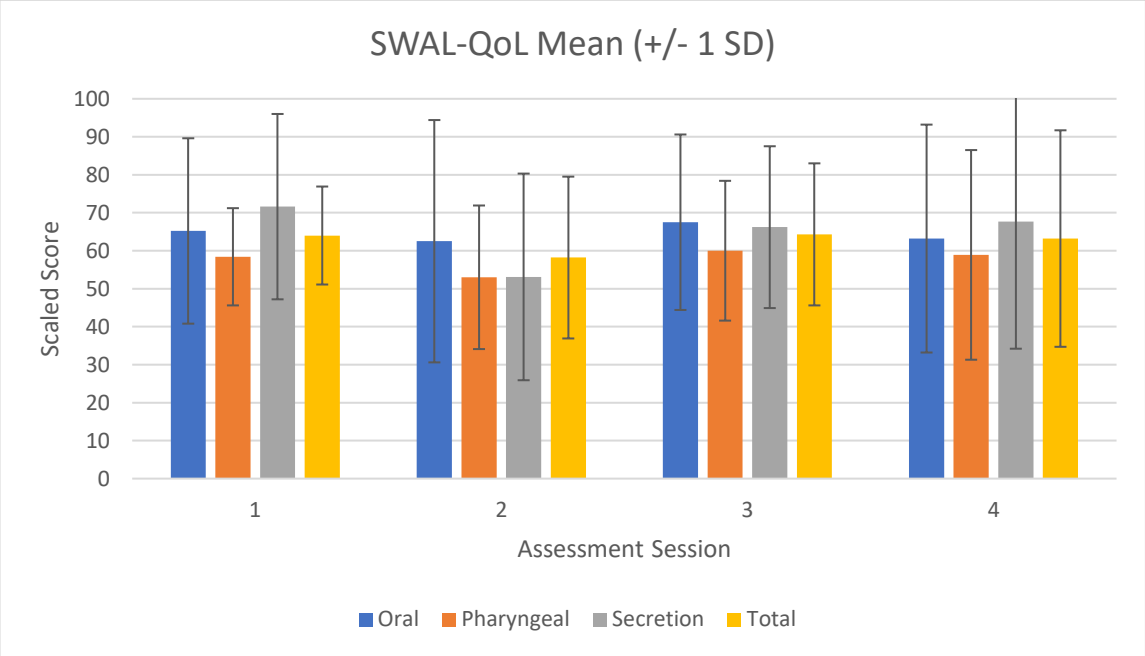

Table E.1

Means and SD of the Timed Water Swallowing Test (TWST) and Timed Test of Masticating and Swallowing Solids (TOMASS)

Assessment	Outcome Measure	Mean (+/- 1SD) Ax 1	Ax 2	Ax 3	Ax 4
TWST	Capacity (mls)	8.55 (8.5)	8.66 (8.7)	7.18 (6.77)	8.41 (8.96)
	Volume (mls)	16.9 (11.9)	17 (11.8)	14.2 (7.36)	14.7 (9.03)
	Time (s)	2.81 (1.38)	2.91 (1.41)	3.01 (1.68)	2.82 (1.68)
TOMASS	Number of bites	3.09 (1.22)	3.27 (1.95)	3.45 (2.81)	3.18 (2.6)
	Number of masticatory cycles	48.7 (22.4)	51.2 (30.3)	52.8 (31.6)	47.2 (28.0)
	Number of swallows	2.36 (1.36)	2.09 (1.04)	2.64 (1.03)	2.64 (0.67)
	Time taken (s)	73.3 (21.7)	79.7 (34.6)	82.4 (39.6)	67.4 (36.3)

Table E.2

Mean and SD of US Measurement of Hyoid Excursion (Percentage Change)

Hyoid Excursion	**Mean (+/- 1SD)**			
(% change)	**Assessment 1**	**Assessment 2**	**Assessment 3**	**Assessment 4**
Dry	20.6 (9.39)	24.0 (8.59)	21.5 (8.03)	23.0 (8.55)
Liquid	25.7 (8.64)	24.1 (6.92)	23.7 (8.48)	23.6 (7.99)
Puree	26.5 (9.57)	25.6 (7.43)	23.0 (8.33)	24.1 (9.13)

Figure E.2

Mean and SD of US Measurements of the Cross-sectional Area of the Submental Muscles: Geniohyoid, Left Anterior Belly of the Digastric (LAB) and Right Anterior Belly of the Digastric (RAB).

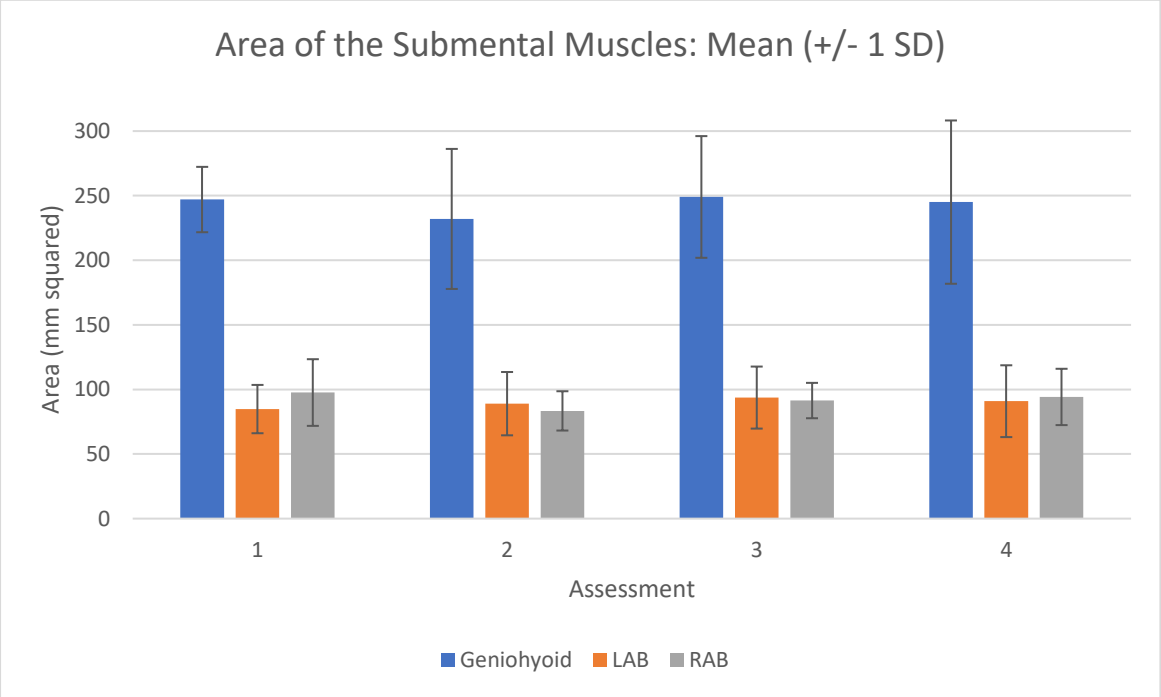

Figure E.3

Mean and SD of VFSS Measurement of Oral Transit Time

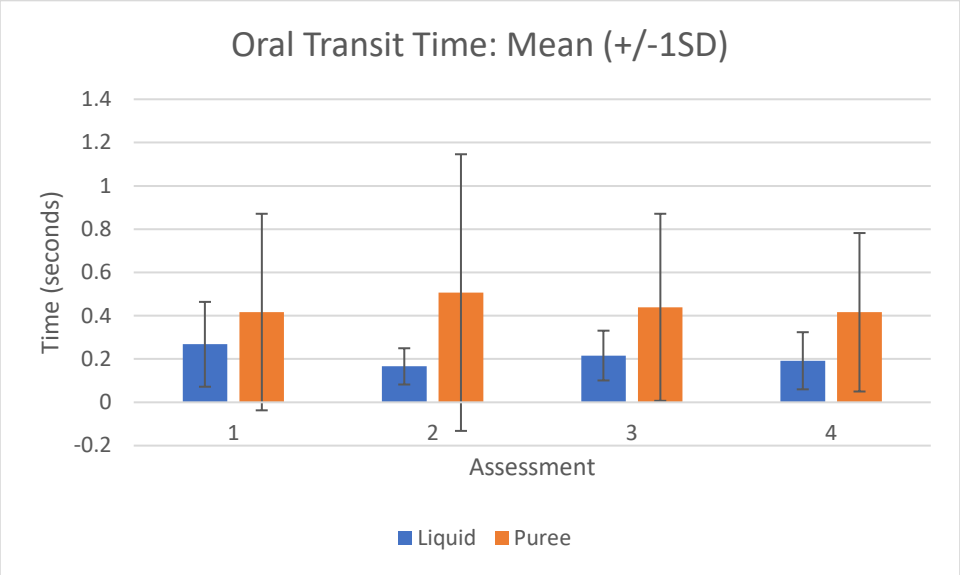

Figure E.4

Mean and SD of VFSS Measurement of Pharyngeal Transit Time

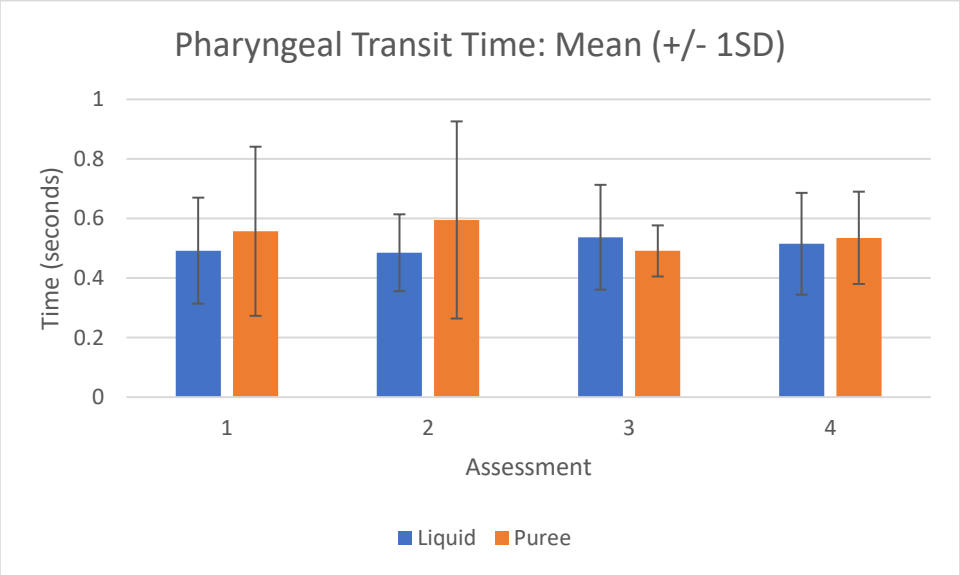

Figure E.5

Mean and SD of VFSS Measurement of Total Transit Time

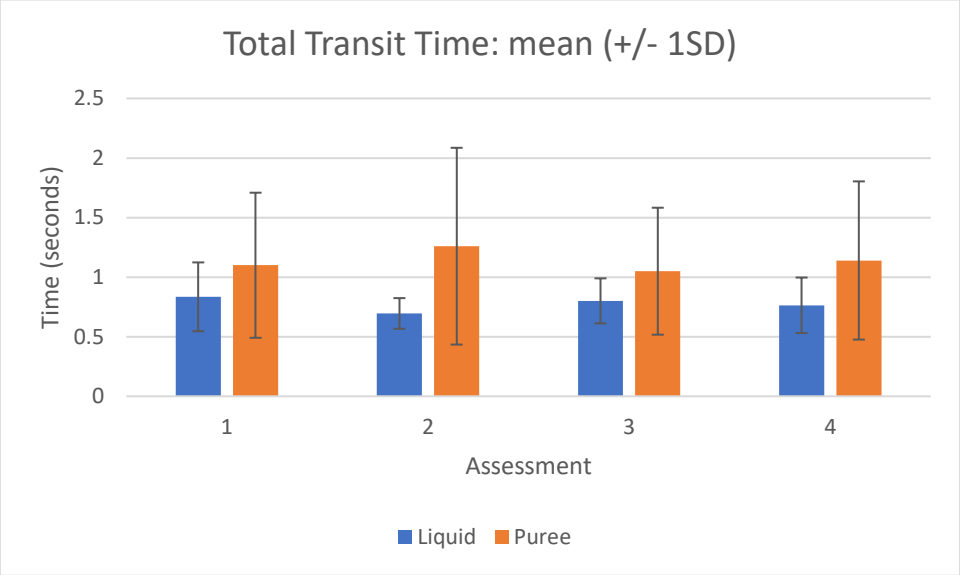

Figure E.6

Mean and SD of VFSS Measurement of Timing of Supraglottic Closure

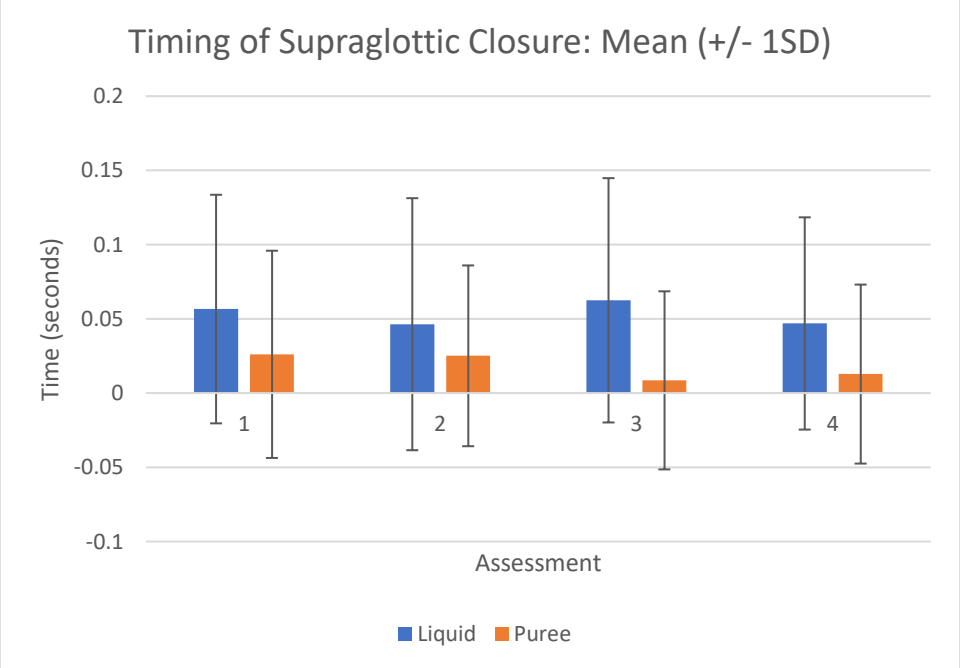

Figure E.7

Mean and SD of VFSS Measurement of Duration of Aryepiglottic Closure

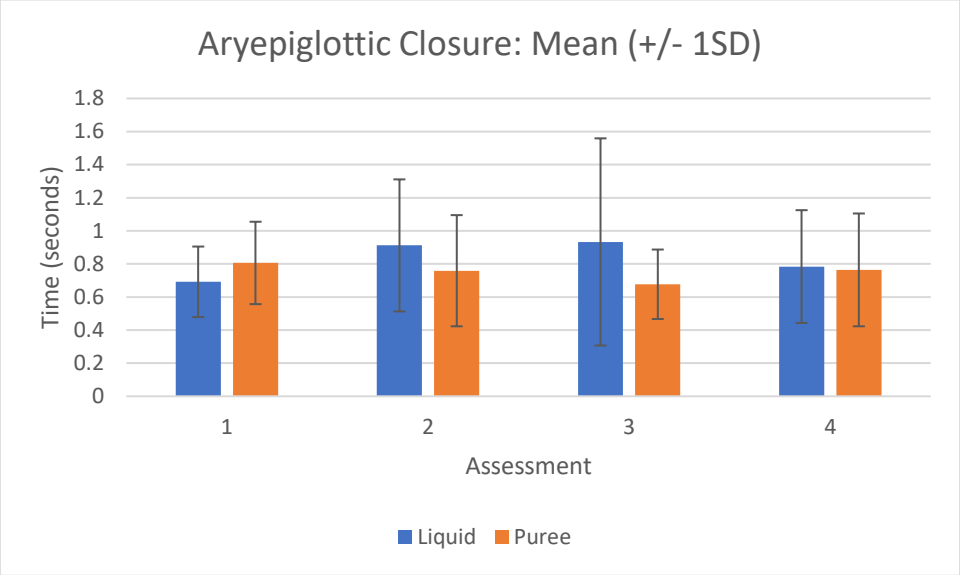

Figure E.8

Mean and SD of VFSS Measurement of Duration of UES Opening

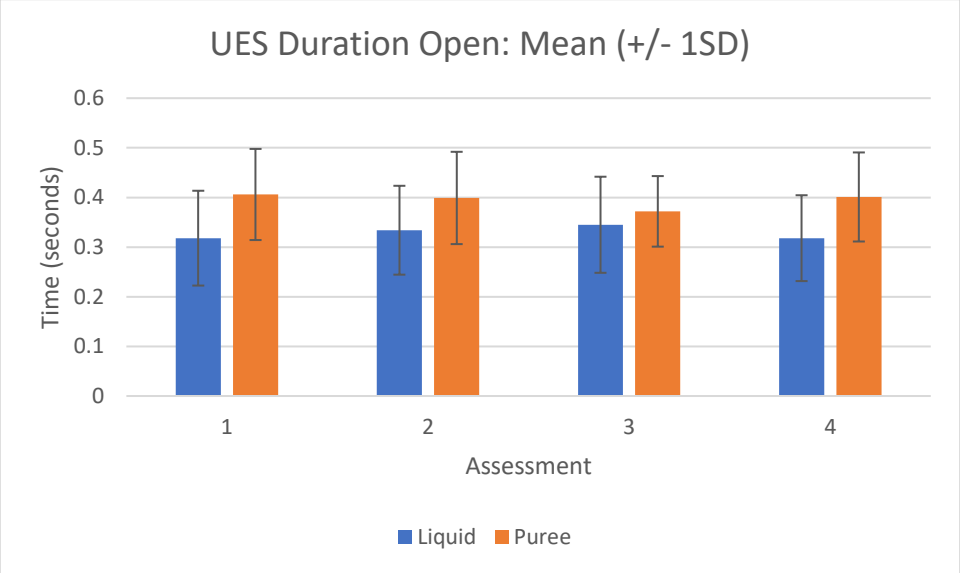

Table E.3

Mean and SD of VFSS Measurement of Hyoid Excursion (mm)

Hyoid excursion	**Mean (+/- 1SD)**			
(mm)	**Assessment 1**	**Assessment 2**	**Assessment 3**	**Assessment 4**
Dry	21.9 (8.44)	18.0 (7.34)	18.5 (7.33)	18.8 (6.62)
Liquid	22.2 (6.69)	21.7 (7.62)	23.8 (8.89)	23.9 (7.00)
Puree	24.1 (6.91)	22.8 (6.26)	21.3 (8.00)	23.5 (8.60)

Table E.4

Mean and SD of VFSS Displacement Measurements: UES Distension (mm) and Pharyngeal Constriction Ratio

UES Distension	**Mean (+/- 1SD)**			
(mm)	**Assessment 1**	**Assessment 2**	**Assessment 3**	**Assessment 4**
Liquid	6.04 (1.26)	6.68 (1.42)	6.72 (2.02)	6.07 (1.37)
Puree	6.96 (1.23)	6.95 (1.47)	6.35 (1.26)	7.01 (1.52)
Pharyngeal Constriction Ratio				
Liquid	0.079 (0.07)	0.057 (0.08)	0.076 (0.07)	0.058 (0.06)
Puree	0.072 (0.09)	0.100 (0.08)	0.105 (0.09)	0.074 (0.07)

Figure E.9

Mean and SD of Manometric Distal Pharyngeal Pressures (mmHg) at Sensor 1

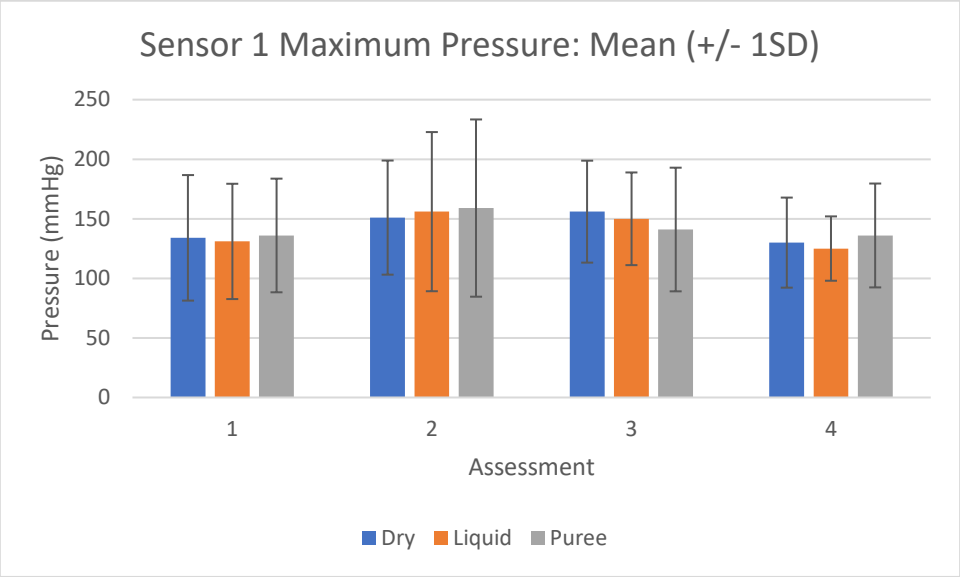

Figure E.10

Mean and SD of Manometric Proximal Pharyngeal Pressures (mmHg) at Sensor 2

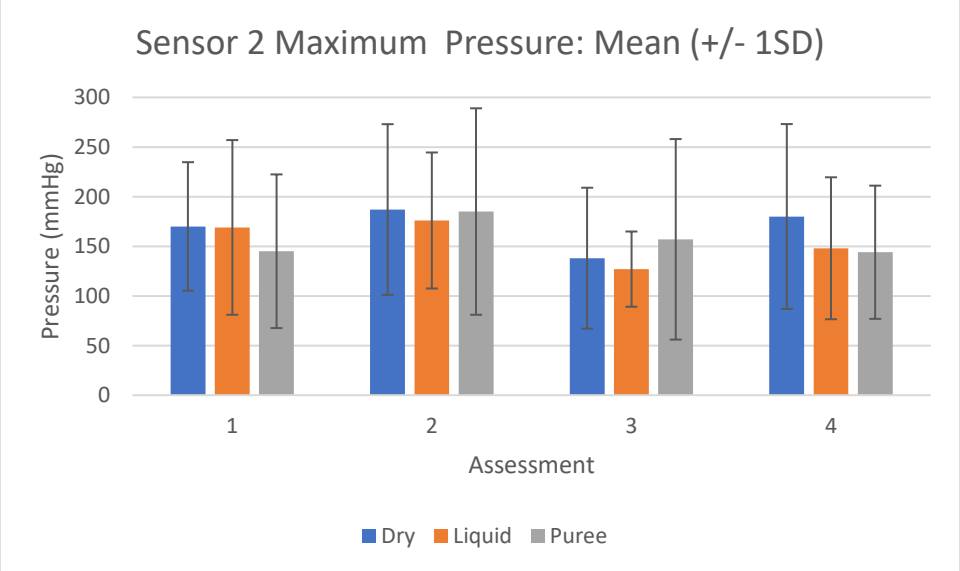

Table E.5

Low Resolution Manometry Descriptive Data

Peak to peak timing (seconds)	**Mean (+/- 1SD) Assessment 1**	**Assessment 2**	**Assessment 3**	**Assessment 4**
Dry	0.17 (0.05)	0.14 (0.12)	0.15 (0.07)	0.12 (0.12)
Liquid	0.15 (0.06)	0.16 (0.07)	0.20 (0.10)	0.17 (0.17)
Puree	0.12 (0.07)	0.16 (0.10)	0.21 (0.05)	0.15 (0.15)
Sensor 3 minimum pressure (mmHg)				
Dry	-6.26 (7.89)	-13.6 (6.3)	-11.9 (5.07)	-14.7 (9.75)
Liquid	-9.34 (8.03)	-12.7 (5.21)	-11.7 (6.56)	-11.7 (11.3)
Puree	-12.3 (7.72)	-13.5 (7.72)	-11.1 (8.01)	-12.1 (8.15)
UES Duration open (seconds)				
Dry	0.78 (0.19)	0.76 (0.18)	0.79 (0.14)	0.73 (0.19)
Liquid	0.83 (0.20)	0.94 (0.28)	0.91 (0.25)	0.75 (0.16)
Puree	0.84 (0.13)	0.96 (0.26)	0.86 (0.23)	0.73 (0.19)

Note. Mean and SD of manometric timing measures (s) and minimal pressure (mmHg) at Sensor 3 representing UES relaxation.

Appendix F – Treatment Study Summary of Effect Sizes

Table F.1

Summary of Effect Sizes for Significant Results Pre-therapy (Assessment 2) to Post-therapy (Assessment 3)

Outcome measure	Pre-therapy (Ax 2) Mean (SD)	Post-therapy (Ax 3) Mean (SD)	Cohen's *d* #
SWAL-QoL (Pharyngeal)	53 (18.9)	60 (18.4)	0.36
SWAL-QoL (Secretion)	53.1 (27.2)	66.2 (21.3)	0.51*
SWAL-QoL (Total)	58.2 (21.3)	64.3 (18.7)	0.29
VFSS Total Transit Time (Liquid bolus) (s)	0.698 (0.129)	0.801 (0.189)	0.62*
VFSS UES Distension (Puree bolus) (mm)	6.95 (1.47)	6.35 (1.26)	0.43

Note. For data with significant treatment effect ($p < 0.05$) Cohen's *d* was used to calculate the effect size of therapy. Cohen's *d* was calculated using the difference in means between pre- to post-therapy, divided by the pooled SD of the means across both assessments. # Cohen's *d* corrected with hedge's *g* for small sample sizes (Lakens, 2013): negligible effect if $d < 0.2$, small effect if $0.2 \leq d < 0.5$, medium effect if $0.5 \leq d < 0.8$, and large effect if $d \geq 0.8$. *Total transit time and Secretion had moderate effect sizes. These results are included in the Appendix as this analysis was not identified *a priori* and was completed post hoc to further interpret the treatment study results.