The role of the primary motor cortex (M1) in volitional and reflexive pharyngeal swallowing

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Abstract

Background and aims:

The primary motor cortex (M1) controls voluntary motor behaviours. M1 has been identified to play a major role in the execution of voluntary corticospinal tasks as well as self-initiated corticobulbar tasks. However, the involvement of M1 in more complex corticubulbar tasks, such as swallowing, is not yet fully understood. Swallowing is quite different from other voluntary motor tasks as it has both voluntary and reflexive components. The degree of M1 involvement in the pharyngeal, or more reflexive, component of swallowing is unclear. Studies investigating the role of M1 in swallowing have yielded contradictory findings regarding the specific functional contribution of M1 to swallowing. Therefore, further investigation is warranted to clarify the role of M1 in pharyngeal swallowing.

Discrete saliva or water swallowing has been utilized in most studies investigating neurophysiology of swallowing in health and disease. However, individuals most frequently complete multiple, consecutive swallows during the ingestion of liquid. Biomechanical differences between discrete and continuous water swallows have been identified using videofluoroscopic swallowing study (VFSS). However, no studies have investigated the pharyngeal pressure differences between these two swallowing tasks. Additional insights into task differences may be revealed through evaluation of pharyngeal pressure utilizing pharyngeal manometry.

This research programme sought to clarify the role of M1 in reflexively and volitionally initiated pharyngeal swallowing. In order to understand M1 involvement in the execution of swallowing, comparative tasks that require known dependence on M1 were also included in this research programme. This research programme addressed the biomechanical changes in motor behaviours as a result of neural disruption during the performance of a number of motor tasks. This neural disruption was intrinsically generated through application of dual task (DT) paradigm and

extrinsically generated using single pulse transcranial magnetic stimulation (TMS). A secondary aim of this research programme was to identify the differences in pharyngeal pressure generation between discrete and continuous swallowing.

Methods:

Twenty-four right handed participants (12 males, average age= 24.4, SD= 6.3) were recruited to this research programme. A number of motor tasks that vary in complexity were tested. These tasks included: volitional swallowing, reflexive swallowing, eyebrow movement, jaw movement and finger tapping with right, left, or bilateral index fingers.

Participants performed multiple trials of several tasks in each study. Repetitions of tasks during a single session may affect performance due to factors such as fatigue or practice. A baseline study was undertaken to determine within-participant variability of measures across repeated trials.

Following the baseline study, the role of M1 in pharyngeal swallowing was investigated in two main studies in counter balanced order. The role of M1 in pharyngeal swallowing was evaluated by investigating swallowing parameters during neural disruption using a DT paradigm. Participants performed tasks in isolation (baseline) and with interference that consisted of pairing swallowing with comparative task that activates M1 (fingers tapping and eyebrow movement tasks).

In the other study, single pulse TMS was utilized to create an electrophysiological disruption to the areas of M1 associated with muscular representation of a number of motor behaviours (swallowing tasks, jaw movement and fingers tapping tasks). Stimulation was provided to both hemispheres in random order to evaluate laterality effects. Swallowing parameters and the performance of the other motor tasks were evaluated when performed with and without electrophysiological disruption.

Differences in pharyngeal pressure generation between discrete and continuous swallowing were investigated using pharyngeal manometry. Pharyngeal pressures were recorded at three locations: upper pharynx, mid-pharynx and upper

esophageal sphincter (UES) during four swallowing types: discrete saliva swallowing, discrete 10 ml swallowing, volitional continuous swallowing, and reflexive continuous swallowing.

The research paradigm used in this research programme identified the effect of experimental conditions on the rate and regularity of task performance. In addition, pharyngeal manometry was utilised to measure the effect of experimental conditions on the pattern of the pharyngeal pressure generation during swallowing. Within subject differences from baseline were identified by means of Repeated Measures Analyses of Variance (RM-ANOVA).

Results:

Initial analysis of the data revealed that repetition of tasks within a session did not affect the rate and regularity of voluntary corticospinal tasks, voluntary corticiobulbar tasks nor swallowing tasks. In addition, repeating the swallowing tasks during a session did not affect pharyngeal pressure as measured by pharyngeal manometry.

When motor tasks were performed concurrently in the DT paradigm, rate and regularity of eyebrow movements were significantly decreased when paired with swallowing tasks, whereas rate and regularity of swallowing were significantly decreased when paired with left finger tapping, but not right finger tapping. However, there was no significant effect of any task on the pattern of pharyngeal pressure generation.

Extrinsically generated disruption using TMS significantly reduced rate and regularity of finger tapping tasks and regularity of jaw movement and swallowing tasks. In addition, interruption of pharyngeal M1 during the volitional swallowing task produced significant increase in the duration but not the amplitude of the pharyngeal pressure.

Pharyngeal pressure generation differed between swallowing types and boluses types, in that saliva swallowing produced longer pharyngeal pressure duration and lower nadir pressure than water swallows. Discrete water bolus

swallowing produced longer UES opening compared to both saliva swallowing or continuous water swallowing.

Conclusion:

The results of this research programme provided valuable methodological information regarding the effect of trials on task performance as well as identifying pharyngeal pressure differences between discrete and continuous swallowing. In addition to the methodological contribution, this research programme expanded on previous knowledge of neural control of swallowing, in that it extended the findings regarding potential role of M1 in pharyngeal swallowing.

Given the absent effect of task repetition on the performance of corticospinal and corticobulbar motor tasks, it is speculated that outcomes of research investigating the effect of experimental manipulation on motor tasks performance is due to the experimental tasks, rather than natural variance in the data.

The effect of swallowing on the rate and regularity of eyebrow movement, when performed concurrently using DT paradigm, suggest bilateral functional overlapping to a significant degree between neural substrates that control swallowing and orofacial muscles. These results offer partial support of bilateral representation of swallowing in the cortex. In addition, results further revealed potential involvement of right M1 in the regulation of pharyngeal swallowing as evidenced by a disruptive effect of left finger tapping on the rate and regularity of swallowing.

The results from the hemispheric TMS disruption study support the active involvement M1 in the execution of voluntary corticospinal and corticobulbar motor tasks. In addition, the current findings extended previous knowledge of neural control of pharyngeal swallowing by documenting the effect of neural disruption on the regularity and pharyngeal pressure measures during volitional and reflexive swallowing. The current programme documented potential role of M1 in the control of pharyngeal swallowing possibly by modulating the motor plan at the swallowing CPG in the brainstem.

This project is the first to document pharyngeal pressure differences between discrete and continuous swallowing. These findings contribute valuable information to the swallowing literature as limited number of studies investigated the biomechanical differences between discrete and continuous liquid ingestion. This knowledge will assist clinicians and researchers in identifying the pharyngeal pressure differences between normal and abnormal swallowing in different swallowing types and ultimately guide their rehabilitation decisions.

Data from this research programme will add to the existing knowledge of neurophysiology of swallowing, thereby facilitating understanding of swallowing pathophysiology which is crucial for appropriate management of swallowing disorders.

Dedication

I dedicate my dissertation work to the soul of my father, Khamis, who passed away just prior to the commencement of this PhD programme. This thesis would have remained a dream had it not been for his encouragement and continuous inspiration to continue my post graduate studies. He will always be remembered.

A special feeling of gratitude to my mother, Ruqia, whose words of encouragement and push for tenacity ring in my ears. My sisters Muna, Sara, Zainab and Maryam and my brother Akeel have provided me with endless support at times when I was about to give up. I am indebted to my family for pushing me to complete this work and travel abroad at the time they needed me the most. All of them are very special and major motivation for the completion of this thesis. This thesis is theirs as much as mine.

I dedicate this work and give special thanks to my lovely wife Latifa for being there for me throughout the entire doctorate program, and for sacrificing a lot in maintaining our relationship and waiting for me patiently over the last four years.

I also dedicate this dissertation to my many friends and extended family who have supported me throughout the process. I will always appreciate all they have done, especially my uncles for looking after my family when I was a way.

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Table of content

Preface

This PhD thesis is presented according to the referencing style recommended by the American Psychological Association Publication Manual (6th ed.). Spelling adheres to the format recommended by the Oxford Dictionary (http://oxforddictionaries.com/).

This research programme was carried out between July 2009 and July 2012 and was undertaken at the University of Canterbury Swallowing Rehabilitation Research Laboratory, located at the New Zeland Brain Research Institute, Christchurch New Zealand. This research was supervised by Dr Maggie-Lee Huckabee, University of Canterbury, Dr Stephanie Daniels, University of Houston, and Dr Sebastian Doeltgen, Flinders University. The University of Canterbury Swallowing Rehabilitation Research Laboratory funded the research expenses. Further financial assistance was provided to the candidate through the Ministry of Higher Education in Oman, and the Departments of Communication Disorders (University of Canterbury).

Preliminary results of this research programme were presented by the PhD candidate at the following conferences and meetings:

- Biomouth Symposium (Christchurch. New Zealand 8-9 June 2010).
- The 8th Asia Pacific Conference (Christchurch. New Zealand 11-14 January 2011).
- Biomouth Symposium (Palmerston North. New Zealand 28-29 November 2011).
- University of Canterbury “PhD in 3” final (Christchurch, 2011)- Awarded first place.
- The Annual Meeting of the Dysphagia Research Society (Toronto. Canada 7-10 March 2012) – (poster presentation).
- The Annual Meeting of the Dysphagia Research Society (Seattle. USA 15-17 March 2013) – (poster presentation).

The following publications were generated during this PhD research:

Full papers:

Al-Toubi, A. K., Abu-Hijleh, A., Huckabee, M. L., Macrae, P., & Doeltgen, S. H. (2011). Effects of Repeated Volitional Swallowing and Rest on the Excitability of Submental Corticobulbar Motor Pathways. *Dysphagia*, *26*(3), 311-317.

Refereed conference abstracts:

Al-Toubi, A. K., Doeltgen, S. H., Daniels, S. K., Corey, D. M., & Huckabee, M. L. (In press). The physiological differences between four types of swallowing measured by pharyngeal manometry in healthy participants [Abstract]. *Dysphagia.* Paper presented at the Annual Meeting of the Dysphagia Research Society, Seattle. USA.

Al-Toubi, A. K., Doeltgen, S. H., Daniels, S. K., Corey, D. M., & Huckabee, M. L. (2012).The effect of electrophysiological disruption to the corticobulbar pathway on the manometric measures of volitionally and reflexively initiated pharyngeal swallowing [Abstract]. *Dysphagia*, 27 (4). Paper presented at the Annual Meeting of the Dysphagia Research Society, Toronto, Orianto, Canada.

Al-Toubi, A. K., Doeltgen, S. H., Daniels, S., Myall, D., & Huckabee, M. L. (2010). The role of the primary motor cortex (M1) in volitional and reflexive pharyngeal swallowing [Abstract]. *New Zealand Dental Journal, 106, (4),* 143. Paper presented in the fourth annual Biomouth Symposium, Christchurch. New Zealand.

Al-Toubi, A. K., Abu-Hijleh, A., Huckabee, M. L., Macrae, P., & Doeltgen, S. H. (2010). Effects of Repeated Volitional Swallowing and Rest on the Excitability of Submental Corticobulbar Motor Pathways [Abstract]. *Dysphagia*, 25, 376. Paper presented the Annual Meeting of the Dysphagia Research Society, San Diego, California, U.S.A.

List of abbreviations

ANOVA	analysis of variance
CN	cranial nerve
CNS	central nervous system
CN V	cranial nerve 5
CN VII	cranial nerve 7
CN IX	cranial nerve 9
CN X	cranial nerve 10
CN XII	cranial nerve 12
CPG	central pattern generator
C_z	cranial vertex
DSG	dorsal swallowing group
DT	dual task
EDM	extensor digitorum muscle
EEG	electroencephalography
EMG	electromyography
FEESS	fibreoptic endoscopic evaluation of swallowing study
fMRI	functional magnetic resonance imaging
ICMS	intra-cortical micro stimulation

M1	the primary motor cortex, Brodmann's area 4
MEG	magnetoencephalography
MEP	motor evoked potential
MRI	magnetic resonance imaging
NA	nucleus ambiguus
NMES	neuromuscular electrical stimulation
NTA	nucleus tractus solitarius
PET	positron emission tomography
RLN	recurrent laryngeal nerve
rTMS	repetitive transcranial magnetic stimulation
S1	sensory strip, Brodmann's area 3
SE	standard error
sEMG	surface electromyography
SLN	superior laryngeal nerve
SMA	supplementary motor area
UES	upper esophageal sphincter
VFSS	videofluoroscopic swallowing study
VSG	ventral swallowing group

Part I: Introduction

Chapter 1: **Introduction**

The primary motor cortex (M1) controls voluntary motor behaviours and has been identified to play a major role in the execution of contralateral voluntary corticospinal tasks (Caroselli, Hiscock, & Bullock, 2006; Springer & Deutch, 1998). In contrast, bilateral activation of M1 was reported in studies investigating self-initiated voluntary movements orchestrated by the corticobulbar motor system.(Avivi-Arber, Martin, Lee, & Sessle, 2011; Kern et al., 2001a; Martin et al., 2004; Sessle, 2009). However, the involvement of the primary motor area in more complex corticubulbar tasks, such as swallowing, is not yet fully understood.

Recently, the role of M1 in swallowing has been investigated using a variety of methods. Some studies report active involvement of M1 in initiation of pharyngeal swallowing (Jefferson et al., 2009; Mistry et al., 2007; Verin, Michou, Leroi, Hamdy, & Marie, 2012). In contrast, other studies report a less active role of M1 in pharyngeal swallowing in that M1 might be activated primarily in the initiation of swallowing related motor tasks with pharyngeal swallowing heavily controlled by swallowing central pattern generator (CPG) at brainstem (Doeltgen, Ridding, Dalrymple-Alford, & Huckabee, 2011; Huckabee, Deecke, Cannito, Gould, & Mayr, 2003; Kern et al., 2001a; Martin et al., 2004). Given these contradictory findings, further investigation is warranted to clarify the role of M1 in pharyngeal swallowing.

Results from previous research utilizing neuroimaging techniques indicate strong asymmetry of sensorimotor representation of swallowing within individuals (Hamdy et al., 1999b; Mosier, Liu, Maldjian, Shah, & Modi, 1999b). However, no agreement has been reached on the dominant hemisphere as different sides of lateralization have been observed across individuals (Humbert et al., 2009; Malandraki, Sutton, Perlman, & Karampinos, 2010) and between swallowing tasks (Dziewas et al., 2003; Kern, Jaradeh, Arndorfer, & Shaker, 2001b; Martin, Goodyear, Gati, & Menon, 2001). Therefore, careful investigation of both hemispheres is warranted in studies which elucidate the role of cortical structures in the swallowing process.

In addition to instrumental methods, a behavioural method, the dual task (DT) paradigm, has also been used in prior research to investigate swallowing lateralization (Daniels et al., 2002; Daniels, Corey, Fraychinaud, DePolo, & Foundas, 2006). Results from both studies support the view of bilateral representation of swallowing with different roles for each hemisphere in the mediation of swallowing. Methodological limitations have been identified in those studies, including the utilization of non-quantifiable tasks, i.e. silent word repetitions and visuospatial line orientation, or pairing tasks that utilize different neural pathways, i.e. swallowing and finger tapping. Therefore, studies utilizing quantifiable motor tasks that share similar neural pathways might yield different results. Furthermore, in both studies employing the DT paradigm, volitional continuous swallowing was tested, which may have input from M1 due to the involvement of oral structures in the execution of this type of swallowing. To date, no studies have investigated the effect of DT paradigm on reflexively initiated swallowing. In addition, further studies utilizing clearer, objective outcome measures, such as pharyngeal manometry or videofluoroscopic swallowing study (VFSS), are needed to further understand the effect of this behavioural paradigm on swallowing biomechanics.

In many studies that have evaluated neural control of healthy swallowing or dysphagic presentation in disordered deglutition, swallowing was tested with discrete water or saliva swallowing. Discrete swallows do not represent typical patterns of ingestive behaviour as most people complete multiple, consecutive deglutitive swallows (Murguia, Corey, & Daniels, 2009). Prior studies have investigated the biomechanical differences between discrete and continuous water swallowing using VFSS (Chi-Fishman & Sonies, 2000; Daniels & Foundas, 2001). However, no studies have investigated the pharyngeal pressure differences between these two tasks. Pharyngeal manometry is the method of choice to investigate the pharyngeal pressure mechanisms during swallowing. It offers excellent temporal resolution providing quantitative data about the pharyngeal and UES pressure generation mechanisms during swallowing (Butler et al., 2009). Such information cannot be inferred from VFSS. Further studies are needed to investigate the biomechanics of continuous swallowing to provide greater understanding in this area.

The aim of this research programme was to clarify the role of M1 in reflexively and volitionally initiated continuous pharyngeal swallowing. To understand the role of M1 in swallowing, comparative tasks that require higher input from M1 were also included in this research programme. These tasks were voluntary corticobulbar tasks that utilize similar neural pathway to swallowing, such as jaw movement and eyebrow movement, and corticospinal tasks, such as index finger movement. The neural control for these movements is well established in the literature. A secondary aim was to identify differences in pharyngeal pressure generation between discrete and continuous swallowing. This research programme addressed the biomechanical changes in motor behaviours as a result of neural disruption during the performance of a number of motor tasks. This neural disruption was intrinsically generated in the DT paradigm and extrinsically generated using single pulse transcranial magnetic stimulation (TMS).

Part I of this thesis provides an introduction to the scope of this project (**Chapter 1**). **Part II** of this thesis consists of two chapters (**Chapters 2 and 3**). **Chapter 2** provides a detailed literature review of previous research in the area of neurophysiology and neural control of various motor behaviours, in particular the neural control of swallowing as it is considered one of the most complex sensorimotor tasks and the primary focus of this research programme. **Chapter 3** presents the hypotheses that were derived from the literature review to be tested in this programme. **Part III** of this thesis highlights the common methodologies used for all experimental studies of this research programme (**Chapter 4**). **Part IV** of this thesis presents, in four chapters, the results of studies undertaken to address the research hypotheses (**Chapters 5, 6, 7 and 8**). During each study, participants were asked to perform multiple trials of several tasks under different conditions which could result in change in performance due to factors such as fatigue or practice. **Chapter 5** presents a baseline study that was undertaken first to examine the effects of task repetition without manipulation on task performance to determine the within-participant variability of measures across repeated trials during a single session. Following the baseline study, the role of M1 in reflexively and volitionally initiated continuous pharyngeal swallowing, was investigated in two main studies undertaken

in counter balanced order. **Chapter 6** presents a study that primarily investigated the contribution of M1 on pharyngeal swallowing using a DT paradigm by pairing swallowing with competitive motor condition that activates M1. **Chapter 7** presents research that investigated the effect of creating electrophysiological disruption, utilizing single pulse TMS, to corticobulbar and corticospinal pathways on motor behaviours along the neuraxis. Motor behaviours ranged from a purely volitional corticospinal movement, i.e., a finger movement task, to reflexive corticobulbar movement, i.e., reflexively initiated pharyngeal swallowing. **Chapter 8** presents a study that investigated the differences in pharyngeal pressure generation between four types of swallowing including discrete saliva swallowing, discrete 10 ml water swallowing, volitionally initiated continuous swallowing, and reflexively initiated continuous swallowing. **Part V** of this thesis merges the findings of the individual chapters into a cohesive discussion of neural control of swallowing (**Chapter 9**) and provides conclusion and future directions (**Chapter 10**) for future studies undertaking similar work. The last part of the thesis (**Part VI)** lists the references used during the completion of this document as well as the appendices.

Part II: Literature review

Chapter 2: **Literature review**

2.1. **Part A: Swallowing biomechanics and neural control:**

Swallowing is a vital element in people's lives as it is not only the primary route for nutrition and hydration but it is highly important in emotions, social identity and quality of life (Morgan & Ward, 2001). A loss or dysfunction of swallowing can result in severe consequences for health and quality of life. Swallowing disorders, e.g., dysphagia, can be the result of many aetiologies that involve a disruption to the neural control of swallowing, the peripheral biomechanics of swallowing or any connection between central and peripheral control of the swallowing system (Paik et al., 2008). Depending on the aetiology, severity of dysphagia can vary from mild, such as a small amount of food remaining in the pharynx, to severe, inability to safely consume any food or liquid by mouth (Bulat & Orlando, 2005). The most common causes of dysphagia include, but are not limited to, stroke (Smithard et al., 1997; Spieker, 2000), neurodegenerative diseases such as Parkinson's disease (Coates & Bakheit, 1997) and Huntington's disease (Kagel & Leopold, 1992), traumatic brain injuries (Mackay, Morgan, & Bernstein, 1999) and tumours within the nervous system or oropharynx (Pauloski et al., 2002). In addition, conditions that may affect peripheral muscles of swallowing such as myasthenia gravis and polymyositis, may also result in swallowing impairment (Ertekin & Aydogdu, 2003).

People can present with dysphagia throughout their life span with a higher incidence of dysphagia reported in the older population; 16 to 22% of the population over 50 years of age is reported to present with varying degrees of dysphagia (Bulat & Orlando, 2005; Kendall & Leonard, 2001). However, the long list of medical conditions that are associated with dysphagia poses difficulty in obtaining accurate statistics of incidence. Incidence of dysphagia following stroke has been thoroughly investigated and the results varied, between 40 to 80%, depending on the diagnostic tools (Martino et al., 2005). When instrumental examination was used for the diagnosis of dysphagia, a higher incidence of 78% was reported following stroke (Daniels & Foundas, 1999); whereas the lowest incidence was reported based on

clinical screening (Splaingard, Hutchins, Sulton, & Chaudhuri, 1988). Other study has investigated the incidence of dysphagia in Parkinson's disease and reported that about 81% of patients with Parkinson's disease experience swallowing difficulties (Coates & Bakheit, 1997). In addition, a study of patients with dementia reported that 84% of this population experience varying degrees of dysphagia (Horner, Alberts, Dawson, & Cook, 1994).

The severe health consequences associated with dysphagia can lead to a substantial reduction in quality of life (Sharp et al., 1999), and consequently the onset of significant psychological effects such as depression (Nguyen et al., 2005). In addition, the resulting health risks from dysphagia are severe and include dehydration and malnutrition (Aslanyan, Weir, Diener, Kaste, & Lees, 2003), pulmonary infection (Martin et al., 1994), aspiration pneumonia (Lee, Pyun, & Jang, 2006; Marik, 2001), and ultimately death (Schmidt, Holas, Halvorson, & Reding, 1994). Dysphagia is also associated with prolonged hospital stay and institutional care (Smithard et al., 1996). It has been reported that the number of patients hospitalized for aspiration pneumonia has increased by 93.5% between 1991 and 1998 (Baine, Yu, & Summe, 2001). Further, aspiration pneumonia was reported to be the most common cause for re-admission to hospitals (Kind, Smith, Pandhi, Frytak, & Finch, 2007). Therefore, the cost of treatment is substantially growing with growth in the number of people suffering from dysphagia and aspiration pneumonia.

In order to understand the pathophysiology of dysphagia, a clear understanding of normal swallowing is warranted. Further, understanding the neural control and biomechanics of swallowing will allow for the identification of disordered swallowing and ultimately facilitate the development of rehabilitation and compensatory techniques.

2.1.1 **Biomechanics of normal swallowing:**

The swallowing process has been divided into multiple phases for ease of explanation of the biomechanics and neural control of this sophisticated process. This

division does not mean total neural or biomechanical independence of these phases. Therefore, the fact that the phases of swallowing are continuous and interdependent should be considered throughout this review. Some authors have divided swallowing into three phases (Miller & Chang, 1999), or four phases (Daniels & Huckabee, 2008; Logemann, 1983; Logemann, Pauloski, & Colangelo, 1998). The three phase model includes an oral phase, pharyngeal phase and esophageal phase (Miller, 1999); however the four phases model added the pre-oral processes as a phase by itself (Daniels & Huckabee, 2008), or divides the oral phase to into an oral preparatory phase and an oral phase (Logemann, 1983). The four phase model of pre-oral, oral, pharyngeal and esophageal phases will be used in this discussion.

2.1.1.1 ***Pre-oral phase:***

The pre-oral phase describes the physiological processes occurring prior to bolus entry to the oral cavity. It is characterized by the physiological effects that result from anticipation, smelling and/or seeing the bolus (Leopold & Kagel, 1997). The sensory information from vision and smell are projected through the respective cranial nerves (CNs) to the cortex for processing (Ross & Nijland, 1998). A number of physiological effects can result from this sensory processing (Maeda et al., 2004) including initiation of salivary flow and elevation of tongue base in anticipation for the bolus (Emond & Weingarten, 1995; Lee & Linden, 1992). In addition, depending on the bolus characteristics, vocal folds adduction may occur during this stage causing swallowing apnoea to protect the airway (Shaker, Dodds, Dantas, Hogan, & Arndorfer, 1990) in particular during the ingestion of liquids due to its fast transit time (Martin-Harris, Michel, & Castell, 2005). These physiological processes play an important role in facilitating the swallowing process.

2.1.1.2 ***Oral phase:***

Upon delivery of the bolus to the oral cavity, a number of biomechanical events occur to accommodate the bolus in the oral cavity. The lips open through the

relaxation of the orbicularis oris muscles to facilitate bolus entrance into the oral cavity (Miller, 1999). The degree of lips opening depends on the size of the bolus. Large boluses require wider opening of the mouth which results in wider opening of the lips. This wider lips opening is facilitated by activation of accessory facial muscles, including levator labii superioris, risorius and zygomaticus (Daniels & Huckabee, 2008). The jaw opens through the activation of jaw opening muscles (includes mylohyoid, anterior belly of digastric and geniohyoid), contraction of the strap muscles of the neck to stabilize the hyoid bone, and relaxation of jaw closing muscles (masseter, pterygoid, temporalis) (Bass & Morrell, 1992). The opposite occurs for jaw closing. To accommodate the bolus in the oral cavity, the tongue grooves at midline (Perlman & Christensen, 1997) and the back of the tongue elevates to approximate with the soft palate and form a glossopalatal seal to prevent pre-mature spillage of the bolus to the pharynx (Daniels & Huckabee, 2008; Logemann, 1983; Miller, 1982; Perlman & Christensen, 1997). Glossopalatal seal is achieved through the activation of a number of muscles including the palatoglossus muscles which elevates the back of the tongue towards the hard palate, styloglossus, stylohyoid and posterior belly of digastric muscles which pull the back of the tongue up and posteriorly (Daniels & Huckabee, 2008). Due the presence of bolus in the oral cavity, the soft palate lowers to facilitate breathing by expanding the nasopharynx. Once the bolus is in the oral cavity, the lips are closed tightly to prevent anterior spillage of the bolus (Miller, 1999).

The manipulation of the bolus in the oral cavity relies heavily on the intrinsic and extrinsic lingual muscles to accommodate the bolus and move it around the oral cavity during the chewing process (Prinz & Lucas, 1995). Bolus manipulation and formation is further facilitated by the saliva produced by the submandibular, sublingual and parotid glands (Prinz & Lucas, 1995; Prinz & Lucas, 1997). Mastication of the bolus is achieved by opening and closing of the jaw, through recruitment of the jaw opening and closing muscles, as well as lateral jaw movement, controlled by the pterygoid muscles, which are required to grind food (Bass & Morrell, 1992). During mastication and bolus formation, the buccinator and the lingual muscles work together to maintain the bolus within the surface of the teeth

and compress the bolus against the palate for formation (Bass & Morrell, 1992; Perlman & Christensen, 1997). The sensory receptors in the oral cavity provide continuous feedback to the sensory centres at the cortex and central pattern generators (CPG) in the brainstem to identify mechanical and chemical characteristics of the bolus (Lund, 1991). Duration of the oral phase could vary depending on these characteristics. Some boluses, such as liquid or saliva, do not require mastication; therefore, oral phase could be abbreviated during the ingestion of those textures (Daniels & Huckabee, 2008). At the end of this phase the base of the tongue lowers and oral transfer begins.

Oral transfer is the action of transferring the cohesive bolus from the oral cavity to the pharynx (Logemann, 1983). Airway protection occurs prior to the initiation of oral transfer and is marked by the intiation of swallowing apnoea (Martin-Harris, Brodsky, Price, Michel, & Walters, 2003), which is achieved through vocal folds approximation (Zamir, Ren, Hogan, & Shaker, 1996). The oral tansfer process starts when the base of the tongue lowers through relaxtion of palatoglossus muscles to eleminate the glossopalatal seal (Perlman & Christensen, 1997). The soft palate then approximates with the posterior pharyngeal wall to form the velopharyngeal seal to protect the nasal cavity and increase pressure in the pharynx (Dodds, 1989), as explained in the pharyngeal phase section of this thesis (section 2.1.1.3). The tongue tip elevates to compress the cohesive bolus against the hard palate, through the activation of intrinsic lingual muscles, to transfer the bolus toward the back of the oral cavity and pharynx by anterior to posterior wave-like motion of the tongue (Dodds, 1989; Ertekin & Aydogdu, 2003). The duration of bolus transfer varies depending on bolus volume (Ertekin & Aydogdu, 2003), however it usually takes less than one second (Daniels & Huckabee, 2008). The oral phase ends when first sign of pharyngeal response begins (Daniels & Huckabee, 2008).

2.1.1.3 ***Pharyngeal phase:***

The pharyngeal phase of swallowing is the most complex phase of the swallowing process as it is characterized by a number of highly coordinated biomechanical events (Kim & McCullough, 2008). These biomechanical events are initiated and controlled through careful integration of neural structures. In order to initiate pharyngeal swallowing, adequate sensory input to the sensory centres at the cortex and swallowing CPG in the brainstem is required (Miller, 2002). The pharyngeal phase consists of a number of well-coordinated biomechanical events completed in less than one second (Kahrilas, Lin, Chen, & Logemann, 1996; Kendall, McKenzie, Leonard, Goncalves, & Walker, 2000; Logemann, 1983). These biomechanical events include: hyolaryngeal excursion, base of tongue to posterior pharyngeal wall approximation, velopharyngeal closure, pharyngeal peristalsis and shortening, elevation and closure of the larynx, and relaxation of the upper esophageal sphincter (UES) (Daniels & Huckabee, 2008). These biomechanical events serve the two main functions of swallowing: accurate transport of the bolus from the oral cavity to the esophagus and assurance of the safety of the airway as explained below.

At the end of the oral phase, the glossopalatal seal is terminated and extrinsic tongue muscles, genioglossus and hyoglossus, activate to lower the base of tongue. The bolus will be pushed to the pharynx by the tongue blade through the activation of styloglossus muscles primarily (McConnel, Cerenko, & Mendelsohn, 1988). This action is of great importance to provide adequate sensory input to initiate pharyngeal response. Upon completion of these biomechanical movements, the tongue continues moving posteriorly to approximate the posterior pharyngeal wall by activation of styloglossus, stylohyoid, posterior belly of digastrics and glossopharyngeus (McConnel et al., 1988). This aproximation provides intial pressure on the decending bolus and also assists the build up of pressure in the pharynx to facilitate bolus transfer. Furthermore, this approximation assists with epiglottic deflection (Khosh & Krespi, 1997). The nasal cavity is protected by velopharyngeal closure during pharyngeal swallowing. This protection is achieved through elevation and retraction of the velum toward the posterior pharyngeal wall (Logemann, 1983). The

velopharyngeal closure is achieved through contraction of levator veli palatini and tensor veli palatini muscles together as well as movement of the posterior pharyngeal wall medially via contraction of palatopharyngeus muscles and contraction of the superior pharyngeal constrictors that comprise the nasopharynx walls. Velopharyngeal closure also plays an important role building the necessary pressure in the pharynx for bolus propulsion (Perlman & Christensen, 1997).

Superior and anterior movement of the hyoid bone and larynx, called "hyolaryngeal excursion" (Perlman & Christensen, 1997), is achieved through contraction of the submental muscles group (anterior belly of the digastric, mylohyoid, and geniohyoid muscles) (Goyal, 1984). This process is further facilitated by contraction of the collective strap muscles, including the thyrohyoid muscles, which are responsible for displacement of the larynx (Goyal, 1984). The submental muscles originate at the mandible, which is usually fixed during the pharyngeal swallowing, and inserted to the hyoid bone; therefore, contraction of this muscles group results in displacement of the hyoid bone in the suprior and anterior direction (Hila, Castell, & Castell, 2001). Given that the hyoid is attached to the thyroid cartilage inferiorly through the strap muscles, the movement of the hyoid bone will influnce similar movement of the larynx. Other biomechanical events result from hyolaryngeal excursion to ensure a safe passage of the bolus through the pharynx. Two of these events are epiglottic deflection, which is crucial for the airway protection, (Perlman, VanDaele, & Otterbacher, 1995) and opening of the UES to allow bolus transfer in to the esophagus (Perlman & Christensen, 1997).

Hyolaryngeal excursion provides the first level of protection to the airway during swallowing through epiglottic deflection (Perlman & Christensen, 1997). Further, anterior-superior movement of the larynx places the larynx under the base of the tongue, providing further protection from the coming bolus (Daniels & Huckabee, 2008). In addition, true and false vocal folds adduct to close the entrance to the trachea and form glottic closure (Daniels & Huckabee, 2008). This glottic closure is considered the primary mechanism for airway protection during swallowing (Medda et al., 2003) and is augmented by anterior rocking of the arytenoid cartilage (Daniels & Huckabee, 2008). Laryngeal closure contributes to increased pharyngeal pressure

to ease the clearence of the bolus through the pharynx (Perlman & Christensen, 1997).

The pharyngeal constrictor muscles that constitute the walls of the pharynx contract in a coordinated manner from top to bottom (Donner, Bosma, & Robertson, 1985). This contraction causes a wave-like motion that clears the bolus from the pharynx by applying positive superior to inferior pressure (Kahrilas, Lin, Logemann, Ergun, & Facchini, 1993). In addition to clearing the bolus, this contraction of the pharyngeal muscles also causes pharyngeal shortening which reduces the distance from the UES.

Relaxation of the UES to accept the descending bolus is the final biomechanical event of the pharyngeal phase of swallowing (Crary & Groher, 2006). The cricopharyngeus muscle that constitutes the major component of UES is tonically contracted during rest to prevent air ingestion into the stomach or redirection of matrials from the stomach to the pharynx (Belafsky, Rees, Allen, & Leonard, 2010; Hila et al., 2001). An inhibitory neural signal must be sent to the cricopharyngeus muscle to cease activation of the UES (Ertekin & Aydogdu, 2003). Upon relaxation, the UES is pulled open due to traction force of the superior and anterior movment of the hyoid bone and larynx (Perlman & Christensen, 1997). The pressure applied by the decending bolus facilitates the opening of the UES (Cook et al., 1992). Bolus transfer from the pharynx to the esophagus is facilitated by the pressure difference between the pharynx and esophagus (McConnel et al., 1988). During the pharyngeal phase of swallowing, there is increasing pressure in the pharynx. The increased pressure in the pharynx is met with negative pressure at the UES as it opens, resulting in a suction force on the descending bolus (McConnel et al., 1988).

2.1.1.4 ***Esophageal phase:***

The esophageal phase begins upon the passage of the bolus tail through the UES (Lang, 2009). Upon entry to the esophagus, the bolus carried to the stomach through esophageal peristalsis and gravity (Donner et al., 1985). The movement of

the bolus through the esophagus is significantly slower than in the pharynx, as bolus moves between 2-4 cm/sec through the esophagus (Schindler & Kelly, 2002). The duration of the esophageal phase can be between 8-15 sec (Miller, 1982). Completion of the esophageal phase is signalled by the entrance of the bolus to the stomach, which is achieved via the relaxation of the lower esophageal sphincter (Lang, 2009; Miller, 1982).

Summary:

The act of swallowing has been divided into the pre-oral, oral, pharyngeal and esophageal phases. The pre-oral phase is characterized by the physiological differences that result from anticipation, smelling and/or seeing the bolus. The oral phase includes preparation of the bolus in the mouth through chewing and manipulation to form a cohesive bolus and then transfer the bolus to the pharynx. The pharyngeal phase characterized by timely elicitation of a number of highly coordinated biomechanical events to safely transfer the bolus from the pharynx to the esophagus without compromising the airway. The esophageal phase involves transferring the bolus from the esophagus to the stomach through esophageal peristalsis and gravity. Any disruption to the biomechanics or neural control of the swallowing cycle could result in a swallowing disorder, aka dysphagia, which could compromise both quality and quantity of life.

A potential limitation in studies investigating the biomechanics of swallowing is that most of the current knowledge has been derived from studies utilizing discrete water or saliva swallowing. However, most people complete multiple swallows during liquid ingestion; therefore, more studies are needed to identify the differences in biomechanical events between discrete and continuous swallowing to further understand the biomechanics of normal liquid ingestion.

2.1.2 **Discrete versus continuous swallowing:**

In most studies of biomechanics, neural control of swallowing or dysphagic presentation in patients with dysphagia, swallowing has been tested primarily with discrete water or dry saliva swallowing. This would appear a gap in the literature given that discrete swallows do not represent typical patterns of behaviour observed during ingestion of liquids. Most people complete multiple, consecutive swallows (Murguia et al., 2009). It is unclear if biomechanical events of continuous swallowing differ from those of discrete swallowing.

Utilizing VFSS, two studies have compared behavioural and mechanical differences between discrete and continuous water swallowing using cup drinking (Chi-Fishman & Sonies, 2000) and straw drinking (Daniels & Foundas, 2001). Continuous swallowing was found to require higher neuromuscular demands to accommodate the increased rate of liquid flow. This increase in the rate of flow required a higher level of movement coordination to ensure safe swallowing (Chi-Fishman & Sonies, 2000; Daniels & Foundas, 2001). Chi-Fisherman and Sonies reported mechanical and sensorimotor differences between continuous and discrete swallowing. A clear example of biomechanical differences between tasks was apparent in laryngeal movement where it was observed that some individuals partially lower the larynx after each swallow before it re-elevates for the subsequent swallow. This movement was essential to accommodate for the greater speed of movement required for continuous swallowing (Chi-Fishman & Sonies, 2000; Daniels & Foundas, 2001). The studies by Chi-Fishman and Sonies (2000) and Daniels and Foundas (2001) both revealed that biomechanical sequences of events were similar during continuous and discrete swallowing. These start with lingual propulsion, followed by hyolaryngeal excursion to protect the airway and end with UES opening. Continuous swallowing behaviour requires repetitive cycles of these events. The repetitive rhythmical cycles in continuous swallowing raise the question of the level of neural control required for such movement. Whether active cortical involvement is needed after the establishment of this rhythmical movement or brainstem regulation is sufficient to regulate such movement is still unknown. Further studies are needed to investigate the neural control of continuous swallowing

to provide greater understanding in this area. A potential limitation in the above mentioned studies is that VFSS does not provide quantitative data about the timing of events of pharyngeal and UES pressure generation mechanisms. Lack of such information produces a gap in the literature and further studies with appropriate outcome measures should be undertaken to clarify if pharyngeal pressure generation differs between discrete and continuous swallowing.

Pharyngeal manometry has been used as a tool to provide quantification of pressure during pharyngeal swallowing. It provides information regarding strength and timing of pharyngeal pressure generation and UES relaxation with excellent temporal resolution (Butler et al., 2009). Pharyngeal manometry has been utilized to investigate pressure differences between discrete saliva and discrete water swallowing (Butler et al., 2009; Castell, Dalton, & Castell, 1990; Cerenko, McConnel, & Jackson, 1989; Olsson, Nilsson, & Ekberg, 1995; Perlman, Schultz, & VanDaele, 1993; Witte, Huckabee, Doeltgen, Gumbley, & Robb, 2008). Contradictory findings were reported in the above mentioned studies. Witte et al. (2008) found that discrete saliva swallows were produced with significantly higher pressure amplitude at the upper pharyngeal sensor and significantly longer pressure duration at the upper and middle pharyngeal sensors compared with discrete water swallows. These findings are in agreement with previous findings from studies utilizing EMG which reported increased muscular effort to initiate saliva swallowing (Sonies, Parent, Morrish, & Baum, 1988) and increased duration of saliva swallowing compared to discrete water swallowing (Hughes et al., 1987). Increased duration of pressure during saliva swallowing was also reported in the study by Perlman et al.; however, the authors reported no significant differences in pressure amplitude between saliva and water swallowing. The increased pharyngeal pressure amplitude and duration during saliva swallowing could be attributed to the small volume and slow flow rate of saliva. Bolus volume has been identified to affect the pharyngeal pressure generation in that lower pharyngeal pressure and shorter duration are needed for boluses with bigger volumes (Butler et al., 2009). Boluses of large volumes utilize weight, velocity and gravity to pass through the pharynx, while boluses of small volume are slower and depend on driving pressure from above to pass through the

pharynx (Butler et al., 2009). The above findings, however, are contradictory to the findings of Castell et al. (1990) who reported shorter duration and tendency towards increased pharyngeal pressure during saliva swallowing. It is noteworthy mentioning that the above mentioned studies utilized different catheter size and sensors; therefore, direct comparison of the results between studies is limited. Castell et al. (1990) used a 4.6 mm catheter with round sensors that measure pressure over 360 degrees while Perlman et al. (1993) utilized 4.6 mm catheter with unidirectional sensors. A smaller catheter (2.1 mm) with unidirectional sensors was utilized in the study by Witte et al. (2008). These differences in catheter size may influence the manometric measures (Brasseur & Dodds, 1991; Dodds, 1987; Lydon, Dodds, Hogan, & Arndorfer, 1975). Increased catheter size has been shown to produce larger variations in the monometric recordings, (Lydon et al., 1975; Olsson et al., 1995; Wilson, Pryde, Macintyre, & Heading, 1989) as well as influencing the bolus flow in the pharynx (Brasseur & Dodds, 1991). Given the above contradictory findings, further studies are warranted to investigate the pharyngeal pressure generation differences between discrete saliva and water swallowing.

Previous studies utilizing pharyngeal manometry to identify the differences in pharyngeal pressure between swallowing types have utilized discrete swallowing (Castell et al., 1990; Perlman et al., 1993; Witte et al., 2008). Discrete swallowing, however, is not the natural mean of fluid ingestion as people swallow continuously during liquid ingestion. Therefore, further studies comparing pharyngeal pressure differences between discrete and continuous swallowing are warranted to facilitate the differentiation between the manometric measures of discrete and continuous swallowing, and to further identify pharyngeal pressure characteristics of normal and disordered swallowing.

Summary:

Discrete swallowing has been utilized extensively in studies investigating the neural control and biomechanical events of swallowing, even though normal ingestive behaviour consists primarily of continuous swallowing. Recent studies have

investigated the biomechanical differences between discrete water and saliva swallowing using pharyngeal manometry and discrete and continuous water swallowing using VFSS. It has been reported that saliva swallowing produces higher pharyngeal pressure than water swallowing and continuous swallowing requires faster neuromuscular reactions to accommodate the increased rate. Further studies with different outcome measures are needed to investigate the biomechanics of continuous swallowing to provide further understanding in this area.

2.1.3 **Peripheral control of swallowing:**

Swallowing involves sophisticated and well-coordinated activation of 32 pairs of muscles (Guyton, 1986), controlled by five CNs and two cervical nerves (Perlman & Christensen, 1997). Most of those CNs consist of two types of fibres: motor fibres, and sensory fibres. Motor fibres carry neural signals from nuclei in central nervous system (CNS) to the peripheral muscles of swallowing. The sensory fibres carry sensory information from peripheral muscles and mucosal surfaces of the oral cavity and the pharynx to the sensory nuclei in the CNS. The CNs that are heavily involved in the control of swallowing are the trigeminal nerve (CN V), facial nerve (CN VII), glossopharyngeal nerve (CN IX), vagus nerve (CN X), hypoglossal nerve (CN XII), pharyngeal plexus (CN IX, CN X), and ansa cervicalis (CN XII, C1, C2) (Figure 2-1).

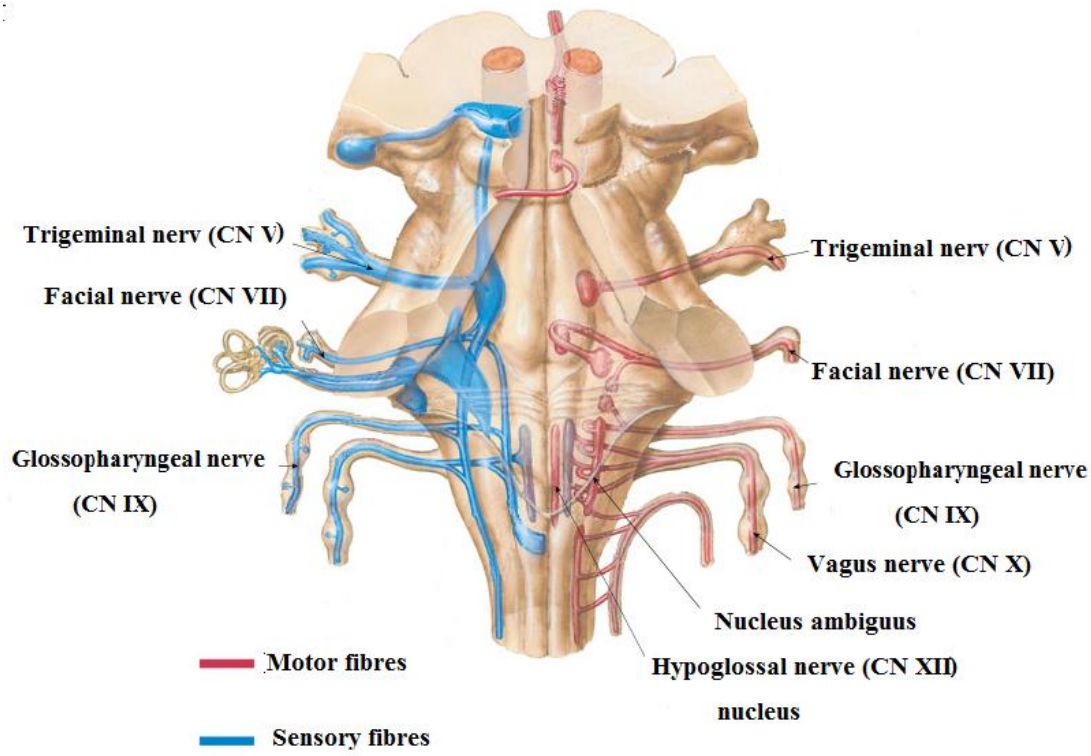

Figure 2-1[1]: Cranial nerve nuclei in the brainstem.

The **trigeminal nerve (CN V)** consists of three branches: the ophthalmic, maxillary and mandibular branches. The maxillary and mandibular branches are of importance to the control of swallowing (Perkins & Kent, 1986). The motor fibres of the mandibular branch innervate the mylohyoid and the anterior belly of digastric muscles which are responible for jaw opening. These muscles play an important role in hyolaryngeal excursion as the two muscles are part of the submental muscles group (Perlman & Christensen, 1997). In addition, the mandibular branch is important for mastication and jaw closing as this branch provides motor innervation to the paired temporalis, masseter, medial pterygoid and lateral pterygoid muscles (Perlman & Christensen, 1997). The sensory fibres of the mandibular branch carries sensory information from the anterior 2/3 of the tongue, lower teeth and gums, while the

[1] Adapted from (Netter, 1972). *Nervous System (The Ciba Collection of Medical Illustrations. Vol.1).* New York: Ciba.

maxilary branch carries sensory information from the hard palate and upper teeth (Perlman & Christensen, 1997).

The facial nerve (CN VII) provides motor innervation to the muscles responsible for facial expression. It contributes to the control of swallowing through motor innervation of the lips (orbicularis oris muscle) and also the accessory facial muscles that assist the spread of the lips for larger boluses (risorius, zygomaticus and quadratus labi superioris) (Daniels & Huckabee, 2008). This CN is important for salivary flow during swallowing through innervation of the submandibular and sublingual salivary glands by the motor fibres of the chorda tympani branch (Daniels & Huckabee, 2008; Perlman & Christensen, 1997). In addition to salivary flow, CN VII provides motor innervation to the paired stylohyoid and posterior belly of the digastric muscles. These muscles are responsible for posterior and superior tongue movement which aid in glossopalatal seal during the oral phase and push the bolus into the pharynx during bolus transfer (Daniels & Huckabee, 2008; Perlman & Christensen, 1997). In addition, this CN also innervates the buccinator muscles which assist in keeping the food in contact with teeth for mastication and formation of bolus (Daniels & Huckabee, 2008; Perlman & Christensen, 1997). The sensory fibres of this nerve are responsible for taste perception from the anterior 2/3 of the tongue (Perlman & Christensen, 1997), as well as sensory information from the soft palate and adjacent pharyngeal wall (Daniels & Huckabee, 2008; Miller, 1999).

The motor fibres of the **glossopharyngeal nerve (CN IX)** innervate the stylopharyngeus muscles which play an important role in pharyngeal shortening during swallowing (Perlman & Christensen, 1997). Furthermore, CN IX innervates the parotid salivary gland which facilitates salivary production (Daniels & Huckabee, 2008). The sensory fibres of this nerve are responsible for the perception of taste from the posterior 1/3 of the tongue (Daniels & Huckabee, 2008), and sensory information from the posterior 1/3 of the tongue, faucial arches and the mucosa lining the oropharynx (Perlman & Christensen, 1997). The sensory fibres of this nerve also play an important role in detecting post swallow residue (Daniels & Huckabee, 2008).

The **vagus nerve (CN X)** plays a vital role in airway protection and the contraction and relaxation of the UES (Ertekin et al., 1995). The superior laryngeal nerve (SLN) and the recurrent laryngeal nerve (RLN), both branches of CN X, are of high importance in the control of swallowing. The motor fibres of the RLN innervate the intrinsic laryngeal muscles to facilitate the vocal fold adduction to protect the airway through innervation of the paired interarytenoid and lateral cricoarytenoid muscles (Daniels & Huckabee, 2008). The sensory fibres of the RLN are responsible for detecting any aspirated materials through the sensory innervation at and below the level of the tracheal bifurcation (Daniels & Huckabee, 2008). The rostral branch of SLN provides motor innervation to cricopharyngeus muscle, which maintains tonic contraction of the UES at rest (Daniels & Huckabee, 2008; Miller, 1982). The sensory fibres of SLN also contribute to the airway protection through sensory innervation of the larynx and proximal trachea, which is important for the activation of reflexive clearing cough (Daniels & Huckabee, 2008).

The hypoglossal nerve (CN XII) is a pure motor nerve that is responsible for the control of tongue movement through the innervation of all intrinsic and many extrinsic lingual muscles (Daniels & Huckabee, 2008; Perkins & Kent, 1986). Therefore, this CN plays an important role in the oral phase of swallowing as it is responsible for activating the muscles required for bolus manipulation in the oral cavity. It also plays important role in controlling the tongue action during the bolus transfer phase.

The pharyngeal plexus (PP) represents a combination of branches from CNs IX and X, and facilitates the formation of the glossopalatal seal through innervation of the bilateral palatoglossus muscles (Daniels & Huckabee, 2008). It further facilitates base of tongue to posterior pharyngeal wall approximation through innervation of the glossopharyngeus muscles, and innervates the levator veli palatine muscles to facilitate velopharyngeal closure (Daniels & Huckabee, 2008). The PP plays a crucial role in supraglottic shortening which is achieved through activation of the paired salpingopharyngeus and palatopharyngeus muscles (Kahrilas et al., 1993). Furthermore, PP contributes to pharyngeal contraction to clear the bolus from the pharynx as PP provide motor innervation to the superior, middle and inferior

constrictor muscles (Kahrilas et al., 1993). The sensory fibres of the PP are responsible for carrying sensory information from the oro- and hypopharynx which assist in identifying the location of the bolus during and post swallowing (Daniels & Huckabee, 2008).

Ansa cervicalis consists of a combination of fibres from CN XII, and two cervical nerves (C1, C2) (Bass & Morrell, 1992) and it is a pure motor nerve. This nerve plays crucial role in hyolaryngeal excursion through innervation of the geniohyoid muscles which are part of the submental muscles group (Daniels & Huckabee, 2008). Ansa cervicalis also provides motor innervation to the strap muscles (paired omohyoid, sternohyoid, sternothyroid, thyrohyoid muscles) which are critical for hyolaryngeal lowering and also assist in jaw opening by stabilizing the hyoid bone (Curtis, Braham, Karr, Holborow, & Worman, 1988).

In summary, swallowing requires a coordinated movement of 32 pairs of muscles controlled by independent CNs and combination of cranial and spinal nerves. The efferent (motor) and afferent (sensory) branches of these CNs facilitate the communication between swallowing areas in the CNS and the peripheral swallowing muscles to ensure safe and efficient swallowing. The complexity of neural control of swallowing is derived from the anatomical complexity of the swallowing system (Donner et al., 1985). A summary of swallowing neural control is warranted to facilitate the understanding of this complex biomechanical process.

2.1.4 **The neural control of swallowing:**

Coordination of the patterned response of swallowing musculature requires precise neural control, which includes input from various sources (Martin & Sessle, 1993; Miller, 1982). These sources include efferent input from swallowing regions in the CNS to activate the swallowing muscles innervated by CNs, and from afferent input from sensory receptors in the peripheral organs to the swallowing nuclei in the CNS (Martin & Sessle, 1993; Miller, 1982). Moving from the peripheral control to

the central control of swallowing, the role of brainstem and the cortex will be discussed respectively.

2.1.4.1 ***The role of brainstem in swallowing:***

Traditionally, the brainstem was thought to play the primary role in the coordination of the pharyngeal phase of swallowing (Jean, 1984a). Previous studies have highlighted the vital role of the brainstem in swallowing and reported that if the nervous system structures located between the trigeminal motor nuclei and C1 are intact, a nearly normal sequential pattern of swallowing can be elicited (Doty, Richmond, & Storey, 1967). In addition, a human foetus is able to swallow by the 12^{th} gestational week, before the development of cortical and subcortical structures (Hooker, 1954). It has also been reported that human anencephalic foetuses are able to swallow (Peleg & Goldman, 1978; Pritchard, 1965). The functional role of the brainstem in swallowing, however, was not clearly understood until the emergence of microelectrode studies in animal models (Lang, 2009). Results from studies utilizing lesion experiments and electrical stimulation to the central and peripheral nervous system in animals have revealed that the CPG for swallowing is situated at the level of the medulla oblongata (Doty, 1968; Doty et al., 1967; Kessler & Jean, 1985; Miller, 1982; Sang & Goyal, 2001).

The nuclei of CNs that innervate the swallowing musculature are located in the brainstem. Microelectrode recordings revealed that motoneurons involved in swallowing are bilaterally represented within the dorsal and ventral medulla and constitute the swallowing CPG (Amri, Car, & Jean, 1984; Doty et al., 1967). The dorsal medulla contains the nucleus tractus solitarious (NTS) and the reticular formation, and they form the dorsal swallowing group (DSG); whereas the ventrolateral medulla hosts the ventral swallowing group (VSG) which consists of neurons in the nucleus ambiguus (NA) and the surrounding reticular formation (Jean, 1984a; Jean & Car, 1979) (Figure 2-2).

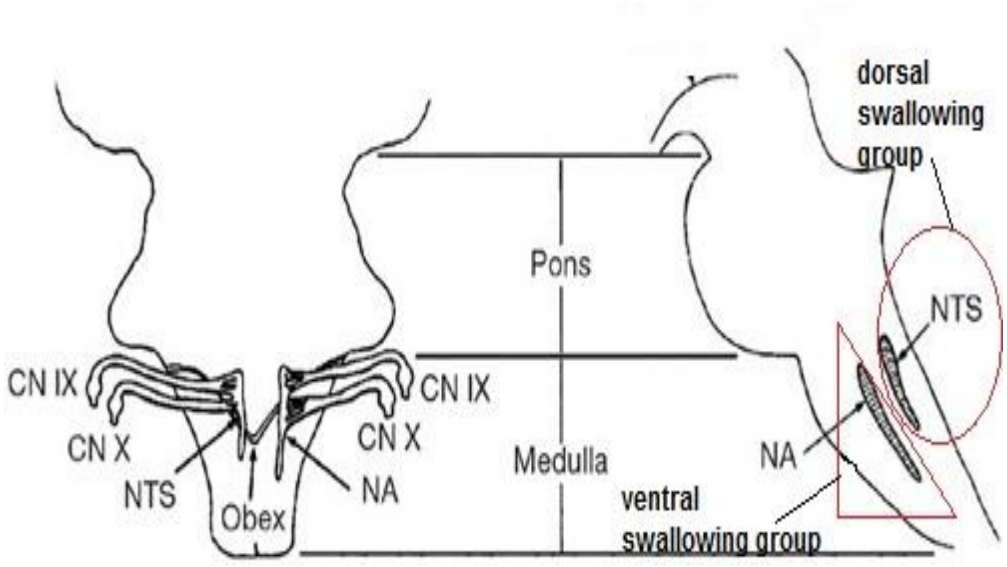

Figure 2-2[2]: Location of the dorsal swallowing group (DSG) and the ventral swallowing group (VSG) in the brainstem.

Dorsal Swallowing Group:

Dorsal swallowing group has been identified to be responsible for initiation and modulation of the swallowing patterned response (Jean, 2001). The activation in this region is dependent on sensory input from peripheral swallowing regions as well as cortical input (Jean, 2001).

The NTS on the DSG contains the primary sensory nucleus for CNs VII, IX and X (facial, glossopharyngeal, and the vagus, respectively) (Daniels & Huckabee, 2008). The DSG also contains afferent connections from the trigeminal sensory nucleus in the pons (Daniels & Huckabee, 2008), which highlights the vital role of this part of the CPG in organizing and planning the swallowing sequence based on the appropriate peripheral information.

[2] *Adapted from Martin-Harris (2006). Coordination of respiration and swallowing. GI Motility online.*

Ventral Swallowing Group:

Connection between VSG and DSG was documented and activation of VSG was found to relay on input from the DSG (Jean, 1984a; Jean & Dallaporta, 2006). Stimulation of the SLN or the frontal cortex have resulted in activation at the VSG region; however, a delay was observed compared to the activation of the DSG (Jean & Car, 1979; Kessler & Jean, 1985). In fact, activation at the VSG region was diminished after lesions involving the DSG (Jean & Car, 1979). Therefore, it has been suggested that the VSG is translating the supplied motor plan to a command sequence for the CNs innervating the swallowing musculature (Jean, 2001).

The VSG contains the NA which is the primary motor nucleus for CNs IX and X (glossopharyngeal and vagus nerves, respectively) (Bhatnagar & Andy, 1995). In addition, the NA has motor projections to primary motor nucleus of the facial (Daniels & Huckabee, 2008; Jean, Amri, & Calas, 1983) and trigeminal nerves in the pons (Amri et al., 1984) and the hypoglossal motor nucleus in the medulla (Amri & Car, 1988). The NTS hosts the primary sensory nucleus for the SLN of the vagus; however, the SLN has also direct connections with the NA (Jean, 2001). This direct connection between SLN and NA has been proposed as a fast and effective way of inducing the reflexive cough response in the event of penetration or aspiration to protect the airway (Daniels & Huckabee, 2008). The ease of eliciting a swallowing response by SLN stimulation could be explained by the direct connection of this nerve branch to both the DSG and the VSG (Doty et al., 1967).

Brainstem networks involved in swallowing control other than the CPG:

The pons also plays a crucial role in neural control of swallowing as it hosts sensory and motor nuclei for some CNs, such as the motor and sensory nuclei of the trigeminal nerve (CN V) (Dodds, 1989). The nuclei of the trigeminal nerve have afferent connections to the DSG (Daniels & Huckabee, 2008), and efferent connections from the VSG (Amri et al., 1984). Furthermore, the trigeminal sensory nucleus also has afferent connections to the thalamus (Perlman & Christensen, 1997).

The trigeminal motor nucleus in the pons receives information from the cortex and the trigeminal sensory nucleus which is responsible for conveying sensory information from a large proportion of the oropharynx (Perlman & Christensen, 1997).

Another nucleus located in the pons is the motor nucleus for the facial nerve (CN VII) (Dodds, 1989), which receives information from the VSG. Jean, Car, and Roman (1975) postulated that the neurons in the pons are a sensory relay for the SLN and glossopharyngeal nerve. The neurons in the pons play a crucial role in providing sensory feedback to higher neural structures and also to the CPG in the medulla during swallowing (Jean, 2001; Jean et al., 1975).

Role of sensory input in altering swallowing program in CPG:

Sensory input from peripheral swallowing regions plays an important role in modulating the central program of swallowing to accommodate the ingested materials in physiologic swallowing (Jean, 1984b, 1990; Kahrilas, 1992). The presence of boluses of various consistencies has been shown to affect the amplitude and latency of the EMG recordings in pharyngeal muscles (Hrycyshyn & Basmajian, 1972). Furthermore, water swallows were found to elicit esophageal peristaltic waves with slower speed and greater amplitude and duration than saliva swallows (Dodds, Hogan, Reid, Stewart, & Arndorfer, 1973; Hollis & Castell, 1975). These results support the concept that swallowing central programs can be modified by means of peripheral input (Falempin, Madhloum, & Rousseau, 1986; Jean, 1984b).

Stimulating peripheral nerves, especially the SLN has been shown to induce a swallowing act (Kessler & Jean, 1985; Miller, 1972). These results indicate that afferent fibres of the SLN might be the main afferent pathway involved in the initiation of swallowing. The afferent fibres from the oral cavity, pharynx and larynx have been shown to travel through the solitary tract and terminate in the NTS (Kalia & Mesulam, 1980). These data suggest that NTS and solitary tract might be the hub for sensory information as it was reported that stimulating the solitary tract and NTS

produced a swallowing response similar to that induced by stimulating the SLN (Kessler & Jean, 1985; Miller, 1972). Furthermore, stimulating the SLN failed to initiate a swallowing response when lesions include the solitary tract were induced (Doty et al., 1967).

Current knowledge about the brainstem control of swallowing have been derived primarily from animal studies, thus a number of limitations should be taken into consideration when interpreting data from these studies (Lang, 2009). Limitations include the anatomical differences between human and animals and differences in muscle fibre composition. Furthermore, most animal studies have used non-physiologic stimuli to activate swallowing phases, and this type of stimuli activates portions of the swallowing phases rather than the entire act. In addition, the data from animal studies were obtained mainly from experiments in decerebrate or anesthetized animals, which could diminish portions of the phases of swallowing; therefore, caution is warranted when drawing conclusions from these studies.

Summary:

Microelectrodes studies in animals have helped to clarify the role of brainstem in swallowing. The brainstem hosts the CNs nuclei for swallowing and the CPG which is responsible for planning and execution of the swallowing. The DSG receives sensory information from afferent nuclei to plan and organize the swallowing sequence. The VSG depends on input from DSG and is thought to be involved in translating the supplied motor plan to a command sequence for the CNs innervating the peripheral swallowing musculature. Sensory input from peripheral swallowing regions was found to play an important role in modulating the swallowing plan at CPG.

2.1.4.2 ***The role of the cortex in swallowing:***

The view of limited involvement of the cortex in swallowing control has been challenged by the ability to voluntarily initiate swallowing without the need to clear a bolus, which suggests that at least some cortical areas may be involved in the initiation of the otherwise brainstem driven swallowing event (Ertekin & Aydogdu, 2003; Hamdy et al., 1996). In addition, it has been reported that repetitive stimulation to specific cortical regions, including M1, resulted in initiation of a swallowing sequence in animals (Jean & Car, 1979). Clinical findings from the stroke population provide further support of upper cortical involvement in the regulation of swallowing as swallowing difficulties are common after bilateral or unilateral hemispheric stroke in the presence of an intact brainstem (Hamdy et al., 1997).

Animal studies utilizing ICMS, reversible cold block, or single neuron recordings in face M1 have contributed important evidence of the functional importance of M1 in the control of swallowing as well as voluntary orofacial movements (Burish, Stepniewska, & Kaas, 2008; Martin et al., 1999; Murray, Lin, Moustafa, & Sessle, 1991; Murray & Sessle, 1992a, 1992b; Yao et al., 2002a; Yao, Yamamura, Narita, Murray, & Sessle, 2002b). Long train ICMS to certain face M1sites was found to evoke different patterns of swallowing and rhythmical masticatory-like movements (Martin et al., 1999; Yao et al., 2002a). In addition bilateral cold block of face M1modified, but did not prevent, masticatory and swallowing movements (Yamamura et al., 2002). These findings revealed that face M1 plays important role not only in the execution of voluntary orofacial tasks but also in more complex patterned responses, e.g., mastication and swallowing, which have been traditionally attributed to brainstem control mechanisms.

The role of the cortex in regulating the swallowing act in humans has been investigated utilizing a number of functional neuroimaging techniques [i.e. functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and magnetoencephalography (MEG)] and neurophysiological measures [i.e. transcranial magnetic stimulation (TMS), repetitive transcranial magnetic stimulation (rTMS) and electroencephalography (EEG)] (Michou & Hamdy, 2009). Multiple cortical areas

have been shown to be regularly activated during swallowing tasks (Kern et al., 2001b; Mosier et al., 1999a; Mosier et al., 1999b). These cortical areas include the *primary sensory (S1) and motor (M1) cortices* (Dziewas et al., 2003; Hamdy et al., 1999a; Hamdy et al., 1999b; Humbert et al., 2009; Kern et al., 2001b; Malandraki, Sutton, Perlman, Karampinos, & Conway, 2009; Martin et al., 2001; Mosier et al., 1999a), *the prefrontal cortex* (Hamdy et al., 1999a; Hamdy et al., 1999b; Humbert et al., 2009; Malandraki et al., 2009; Martin et al., 2001), *the insula* (Dziewas et al., 2003; Hamdy et al., 1999a; Hamdy et al., 1999b; Humbert et al., 2009; Kern et al., 2001b; Malandraki et al., 2009; Martin et al., 2001), *and the anterior cingulate cortex* (Hamdy et al., 1996; Hamdy et al., 1999a; Hamdy et al., 1999b; Kern et al., 2001b; Martin et al., 2001; Mosier et al., 1999b). The primary sensorimotor cortex, which includes pre-motor cortex, supplementary motor area (SMA), M1 and S1 has been reported to be the most consistent area of activation across various studies investigating swallowing task.

A meta-analysis study by Sörös, Inamoto, and Martin (2009) reported distinct yet overlapping neural network representation of voluntary water and voluntary saliva swallowing. They summarise that water swallowing produced high activation in bilateral sensorimotor cortex, right inferior parietal lobule, and right anterior insula. Saliva swallowing, however, produced high activation in left sensorimotor cortex, right motor cortex, and bilateral cingulate gyrus. These results suggest differences in neural control between bolus types. These differences could be attributed, at least in part, to differences in bolus properties given that water boluses were of greater volume and colder than saliva. Future studies should examine if different swallowing and bolus types produce differences in neural control and biomechanical responses.

Even though multiple cortical areas have been identified to be activated during swallowing tasks, the functional contribution of each of those areas in the regulation of swallowing is not clearly understood. EEG has been utilized to investigate cortical motor planning prior to swallowing (Huckabee et al., 2003; Satow et al., 2004) with the SMA identified to play an important role in volitional swallowing. However, results regarding SMA contributions to reflexive swallowing

cannot be derived from the above studies as an isolated reflexive swallowing task was not utilized.

Activation of multiple cortical areas, in particular SMA, M1 and S1, was reported during the volitional swallowing and swallowing related tasks using fMRI (Hamdy et al., 1999a; Kern et al., 2001a; Malandraki et al., 2009; Martin et al., 2007; Martin et al., 2001; Martin et al., 2004) and PET (Hamdy et al., 1999b; Zald & Pardo, 1999). It has been reported that this cortical involvement is largely due to the regulation of voluntary aspects of swallowing. In fact, larger activation was observed during voluntary tongue movement task than during volitional swallowing task (Martin et al., 2004). A reflexive swallowing task was not included in the above studies; therefore, the potential involvement of these cortical areas in regulating pharyngeal phase of swallowing cannot be eliminated.

Studies utilizing reflexive and volitional swallowing tasks revealed potential cortical involvement beyond the voluntary control of swallowing as bilateral activation was observed, in particular in M1 and S1, during both swallowing tasks (Kern et al., 2001b). Larger total volume of activation was observed during volitional swallowing and was attributed to the increased oral motor effort required during volitional swallowing which was minimized during reflexive swallowing. Even though volitional effort was minimized during the reflexive swallowing task, the anticipation of direct infusion of water to the pharynx may have yielded anticipatory protective movements in the oral cavity, in particular tongue movement, which could have contributed to the activation observed in M1 and S1.

In an attempt to eliminate the effects of anticipation and awareness on cortical activation during imaging studies of swallowing, Martin et al. (2001) compared cortical activation observed in fMRI during naïve swallowing to that observed during volitional saliva swallowing and 3 ml water bolus swallowing. Activation of lateral M1, S1 and right insula was observed during the three swallowing conditions. Reduced activation was observed in the caudal anterior cingulated cortex during naïve swallowing. This area was found to be responsible for the processing of sensory, motor and cognitive information (Devinsky, Morrell, & Vogt, 1995). The

data in this study provided evidence that M1, S1 and the right insula are involved in both volitional and reflexive swallowing tasks. The temporal resolution of the fMRI poses a limitation of sequential activation of cortical areas in studies utilizing fMRI (Sack, 2006); therefore, it is difficult to infer causal-function relationship from studies utilizing fMRI. Further details regarding the limited temporal resolution of fMRI is discussed in the section (2.2.1.1) of this chapter.

To overcome the limited temporal resolution of fMRI, MEG was used to assess cortical input during swallowing (Dziewas et al., 2003; Furlong et al., 2004). MEG offers greater temporal precision, allowing more specific investigation of cortical activation patterns during the rapidly sequenced swallowing processes. Activation of M1 was observed when participants were asked to replicate oral preparatory movements by pressing their tongue against the hard palate (Furlong et al., 2004). Activations of M1 and SMA were observed during volitional water swallowing in the same study. The authors suggested significant involvement of the primary sensorimotor cortex in the motor control during oral phase of swallowing. This study; however, did not investigate the possible contribution of M1 in reflexive swallowing. Utilizing the same technique, Dziewas et al. (2003) expanded the Furlong et al. and added a reflexive swallowing task. Reflexive swallowing was initiated by transnasal injection of water into the pharynx. Results indicated activation in the M1 and S1 representations corresponding to the tongue during the tongue pressing task and volitional swallowing task. However, activation of S1 and M1 was located more medially during the reflexive swallowing task, suggesting representation of more inferior muscles (Dziewas et al., 2003), such as those of the pharynx (Hamdy et al., 1996). Even though MEG has greater temporal resolution than other nuero-imaging studies, this technique has limited spatial resolution which limits the information obtained from subcortical structures that are likely to be involved in swallowing (Dziewas et al., 2003). The result of this study revealed potential cortical involvement, in particular M1 and S1, in the regulation of reflexive, pharyngeal, swallowing; however, the functional role of these cortical areas remains unclear.

A study utilizing TMS to induce motor evoked potential (MEP) from the submental muscles revealed that MEPs were frequently detected with larger amplitude during the volitional contraction of the target muscles, less frequently detected with smaller amplitude during the volitional swallowing task, and infrequently detected during the reflexive swallowing task.(Doeltgen et al., 2011). The authors hypothesized that M1 marginally involved in reflexive swallowing signifying increased level of brainstem control for this task compared to volitional swallowing and volitional contraction. As MEPs were still measurable during the reflexive swallowing task, this study offers further support for primary sensorimotor cortex input beyond the volitional components of swallowing. However, it was hard to quantify the level of oral phase movement inhibition during the swallowing tasks, in particular during the reflexive swallowing task. Furthermore, these results could be a representation of the degree of the floor of mouth muscles involvement in the execution of the research tasks, rather than degree of M1 involvement, as EMG amplitude was not compared during the execution of experimental tasks.

In summary, the role of the cortex in swallowing has been investigated extensively. Multiple cortical areas have been shown to be activated including the anterior cingulate gyrus, the premotor and motor cortices, and the insular cortex. This activation has been observed during the performance of volitional swallowing and swallowing related motor tasks particularly in M1 and S1, suggesting active involvement of these areas in the regulation of those tasks. More medial activation was observed during reflexive swallowing tasks compared to volitional swallowing tasks suggesting potential involvement of M1 and S1 in the control of reflexive swallowing. The functional contribution of each neural area in regulating swallowing is not clearly understood in particular the role of M1 in the reflexive pharyngeal swallowing is not clearly defined.

The functional contribution of M1 in swallowing:

A number of studies have attempted to clarify the functional contribution of M1 in swallowing. Creating electrophysiological disruption to the area of M1 representing the pharyngeal muscles that involved in swallowing has been one of the techniques used to investigate the role of M1 during pharyngeal swallowing. High intensity 1 HZ rTMS was applied over M1representation of pharyngeal muscles to induce "virtual lesion" and clarify its role in modulating swallowing behaviour (Jefferson et al., 2009; Mistry et al., 2007). Results from both studies revealed faster initiation of swallowing response following the application of rTMS to the hemisphere that induced larger MEP responses only (dominant hemisphere). This effect was reversed by application of 5 Hz excitatory rTMS to the contralesional hemisphere suggesting possible involvement of the non-dominant hemisphere in mediating pharyngeal swallowing (Jefferson et al., 2009). Based on the results of the above mentioned studies, the authors postulated that M1 might play an inhibitory role in swallowing. Reducing M1 excitability, as result of inhibitory rTMS stimulation, led to faster initiation of swallowing in healthy adults. These findings are contradictory to findings from the stroke population where delayed pharyngeal swallowing, as identified by VFSS, is a common problem in lesions of the primary motor cortex (Kidd, Lawson, Nesbitt, & Macmahon, 1993; Power et al., 2007). The major difference between studies utilizing experimentally induced virtual lesions and those involving the stroke population is that many hemispheric sites could be affected in stroke; therefore, it is hard to link swallowing abnormality to specific brain site (Hamdy et al., 1999a). A potential confound in the studies by Mistry et al., and Jefferson et al. is that the authors did not control for the possibility of faster cognitive processing of the external cue. More reliable outcome measure of the changes in swallowing biomechanics following the application of rTMS, such as VFSS or pharyngeal manometry, could have strengthened the findings of these studies.

Verin et al. (2012) utilized high intensity 1 HZ rTMS to induce "virtual lesions" over pharyngeal muscle representation on M1. The dominant and non-dominant hemispheres were investigated in different sessions with one week interval.

The authors utilized VFSS as an outcome measure to further investigate the functional effect of these experimental. Stimulating the dominant hemisphere resulted in an increase in swallowing response time and a decrease in oral transit time 5 mins after the stimulation. These physiological changes recovered rapidly and normal swallowing was observed 30 mins following the stimulation. These findings provide further support to the involvement of M1 in controlling the timing of pharyngeal swallowing (Mistry et al., 2007). Furthermore, stimulating the non-dominant hemisphere resulted in decreased oral transit time. The decrease in oral transit time when both hemispheres were stimulated provides further support of bilateral M1 involvement in regulating the oral phase as reported in previous neuroimaging studies (Gallas, Marie, Leroi, & Verin, 2009; Martin et al., 2004).

The findings of delayed pharyngeal swallowing are in agreement with the preliminary findings of Humbert (2010) who utilized single pulse TMS over the M1 representation of the laryngeal muscles to create a transient disruption during swallowing. TMS produced a delay in the initiation of swallowing related EMG activity compared to swallowing without TMS. The delay ranged between 1-125 msc, suggesting large individual variability in the response to TMS. Therefore, one might argue that the delay observed in this study might be due to the normal variability in the initiation of pharyngeal swallowing among healthy adults (Martin-Harris, Brodsky, Michel, Lee, & Walters, 2007).

The findings of increased swallowing response time observed in the study by Verin et al. (2012) are contradictory to the findings of Mistry et al. (2007) and Jefferson et al. (2009) who reported a decrease in swallowing reaction time following stimulation to the dominant hemisphere. The contradictory findings between these studies could be due to differences in methodology. Mistry et al. and Jefferson et al. applied rTMS for 10 mins compared to 20 mins in Verin et al. study. The volume of the ingested bolus was also different between studies, 5 ml provided in Verin et al. study and 3 ml provided in Mistry et al. and Jefferson et al. studies. The protocols of identifying swallowing response time were different as well. While Mistry et al. and Jefferson et al. used a reaction time protocol in response to external cue, Verin et al. used VFSS to quantify this parameter. These methodological differences hinder direct

comparison of the results, which contributes to the ambiguity of the role of M1 in controlling pharyngeal swallowing. Although potential involvement of M1 in the timing of pharyngeal swallowing is suggested in the above studies, none of the studies investigated the contribution of M1 in the pharyngeal biomechanics and pressure generation in the pharynx. Further studies are warranted to clarify this issue. The studies reviewed support the feasibility of utilizing single pulse TMS and rTMS techniques to investigate neural structure-function relationships. Given that single pulse TMS creates focal disruption to neural areas, further studies should utilize this technique to investigate the contribution of different neural areas in swallowing control. More details on the underlying mechanisms of TMS effect will be provided in section 2.2.1.2 of this thesis.

2.1.4.3 ***Asymmetry of swallowing representation in the brain:***

Functional hemispheric lateralization of swallowing was suggested by clinical findings. Robbins and Levin (1988) and Robbins, Levine, Maser, Rosenbek, and Kempster (1993) reported that oral stage dysphagia may be more apparent in left hemisphere dysfunction, while right hemisphere damage may result in pharyngeal stage dysmotility and aspiration. Some studies that investigated particular lesion localization offered partial support for these findings. For example, Daniels, Foundas, Iglesia, and Sullivan (1996) found that right hemisphere damage was associated with pharyngeal stage difficulties. However, the authors did not identify oral stage dysmotility associated with left hemisphere damage. Therefore careful investigation of both hemispheres is warranted in studies investigating the role of different cortical structures in the swallowing process.

Bilateral activation of M1 has been reported during swallowing tasks. However, some studies reported hemispheric lateralization independent of handedness during different phases of swallowing. For example, volitional swallowing showed more lateralization to the left hemisphere compared to the reflexive swallowing (Furlong et al., 2004; Martin et al., 2004; Michou & Hamdy, 2009). Strong asymmetry of sensorimotor representation was reported within

individuals (Hamdy et al., 1999a; Hamdy et al., 1999b; Mosier et al., 1999a). However, no agreement has been reached on the dominant side of lateralization as mixed results were observed across individuals (Hamdy et al., 1999a; Hamdy et al., 1999b; Martin et al., 2001; Martin et al., 2004). A study utilizing MEG found stronger left hemispheric activation of the sensorimotor cortex and insula; however, the degree of lateralization was dependent upon task complexity (Dziewas et al., 2003). Strong left lateralization was apparent in volitional swallowing; less lateralization was reported with reflexive water swallowing, and no lateralization was observed during a tongue movement task. In contrast, Kern et al. (2001b) utilized fMRI and reported that volitional swallowing induced greater right hemispheric activation, whereas the opposite was observed in a reflexive swallowing task. Based on the previous results, asymmetry of swallowing function appeared to vary between individuals (Humbert et al., 2009; Malandraki et al., 2010; Martin et al., 2001) and between tasks (Daniels et al., 2002; Daniels et al., 2006; Dziewas et al., 2003; Kern et al., 2001b; Mosier et al., 1999a); therefore, hemispheric lateralization for swallowing should be investigated on an individual basis.

Given the uncertainty surrounding the issue of swallowing lateralization, DT paradigm was utilized to investigate lateralization of swallowing in a group of right-handed adults (Daniels et al., 2002; Daniels et al., 2006). Daniels et al. (2002) paired swallowing with rapid index finger tapping to determine hemispheric specialization in swallowing. In addition, a language condition, which is left hemisphere specific, was also included in this study. Participants performed two tasks concurrently in the DT condition in randomized order. The performance during DT conditions was compared to performing tasks in isolation. Significant interference of word repetition on finger tapping from both hands was reported, with the interference being greater in the right hand. Furthermore, significant interference of finger tapping from both hands was also found during concurrent swallowing tasks. The volume per swallow was significantly lower during silent word repetition but not during finger tapping tasks. The authors provide partial support for the bilateral representation of swallowing with possible greater left hemisphere involvement. A limitation of this study as reported by the authors was that they did not adequately address the potential

contribution of the right hemisphere, as a right hemispheric specialized task comparable to word repetition was not employed.

Daniels et al. (2006) expanded the design of the earlier study (Daniels et al., 2002) by adding a right hemisphere lateralized task (visuospatial line orientation task). Significant effect of word repetition on volume per swallow was reported, as it was significantly lower than at baseline or with right and left finger tapping tasks. Number of swallows was significantly lower when swallowing was paired with finger tapping conditions than at baseline, but not when paired with the word repetition task. There was a significant effect of a visuospatial line orientation task on number of swallows but not volume per swallow. Swallowing interference did not affect finger tapping of both hands in this study. Given the above results, it was hypothesized that the two hemispheres have different roles in swallowing behaviour (Daniels et al., 2006). The effect of the lateralized left hemisphere task of silent word repetition on volume per swallow suggests that left hemisphere may play a role in the volitional, oral phase of swallowing. In contrast, the significant effect of the lateralized right hemisphere task on number of swallows suggests involvement of this hemisphere in the more reflexive pharyngeal phase of swallowing. The authors postulated that finger tapping interference with the timing of swallowing (reduced number of swallows) could be due to the overlapping of anatomical networks between finger tapping and swallowing representations in the primary motor cortex. This effect could be due to the fact that using two motor tasks would involve similar cortical areas such as M1, thus greater demand for resources would be expected than when pairing motor task with cognitive task. Interestingly, some of the results obtained by Daniels et al. (2002) appear contradictory to the findings of Daniels et al. (2006). Daniels et al. (2002) reported that finger tapping with both hands was affected significantly during concurrent word repetition and during concurrent swallowing; however, there was no significant effect of concurrent finger tapping on swallowing. These findings were contradictory to the findings of Daniels et al. (2006) where concurrent swallowing tasks did not significantly affect finger tapping, however concurrent finger tapping significantly affected the number of swallows. Sample size was different between the two studies 14 subjects in Daniels et al. (2002) and 38 subjects in Daniels et al.

(2006). Therefore, the larger sample size in the latter study might have contributed to these findings. This trade-off between finger tapping and swallowing effects in both studies might support the theory that swallowing is bilaterally represented. Daniels et al. support the view of bilateral representation of swallowing with different roles of each hemisphere to mediate swallowing.

A major methodological limitation in the above studies is utilizing tasks that are not quantifiable, such as silent word repetition and visuospatial line orientation. Therefore, effects of the DT on these tasks cannot be evaluated. Even though it is well established that the left hemisphere has a major role in controlling language, especially in right-handed adults (Kinsbourne & Hicks, 1978) and visuospatial line orientation is associated with right hemisphere (Benton, Hannay, & Varney, 1975; Warrington & Rabin, 1970), the validity of these tasks is challenged given that it is impossible to objectively measure the performance of these tasks. In order to increase the confidence in verifying the lateralization patterns, both tasks in DT paradigm should be quantified. Measuring the performance of both tasks will enable the measurement of prioritization in task selection and performance between tasks as indicated by the degree of interference in the performance of one or both tasks. Furthermore, pairing two motor tasks that utilize different neural pathways, such as finger tapping (utilizing corticospinal pathway) and swallowing (utilizing corticobulbar pathway), could be one of the confounds in studies utilizing DT. Studies evaluating two motor tasks that utilize similar neural pathways are needed to identify if pairing two motor tasks that that utilize similar neural pathways results in greater interference. This will provide a clearer representation of task prioritization and competition for neural resources. Furthermore, Daniels et al. have carried multiple statistical analyses without correcting for the inflation of type I error. The authors reported that they were willing to accept the inflation of the error due to the exploratory nature of this research at the time.

Summary:

The role of M1 in swallowing has recently been investigated using a variety of methods. Contradictory findings were reported regarding the involvement of M1 in the pharyngeal phase of swallowing. Given the contradictory findings in the role of M1 in regulating swallowing, a number of researchers have suggested that M1 might be activated primarily in the initiation of swallowing related motor tasks with the rest of the swallowing process heavily controlled by swallowing CPG in brainstem. However, studies utilizing neural disruption to pharyngeal M1 have revealed active involvement of M1 in regulating the timing of pharyngeal swallowing through a balance of excitatory or inhibitory mechanisms. The neural disruption studies focused on the initiation and the timing of pharyngeal swallowing; however, no studies investigated the effect of neural disruption on the biomechanics of pharyngeal swallowing. Strong asymmetry of swallowing function has been reported within individuals. However, no agreement has been reached on the dominant side of lateralization as mixed results were observed across individuals and tasks. The possibility of bilateral representation of some components of swallowing could not be ignored, warranting careful investigation of both hemispheres in studies investigating the neural control of swallowing.

2.1.5 **Neural control of voluntary corticobulbar movements:**

2.1.5.1 ***Role of M1 in the execution of voluntary corticobulbar tasks:***

The involvement of M1 in the control of corticobulbar tasks depends on the level of volition required to execute these tasks. Self-initiated voluntary tasks depend mainly on input from M1 and secondarily on input from other cortical or subcortical areas such as pre-motor cortex, SMA, basal ganglia and cerebellum (Klineberg & Jagger, 2004; Martin et al., 2004; Sessle, 2009; Sessle et al., 2005). In contrast, reflexive orofacial movements depend mainly on brainstem neural circuits (Avivi-Arber et al., 2011). Execution of tasks that involve volitional and reflexive components, however, require input from cortical, subcortical, and brainstem neural

circuitries (Lund & Kolta, 2006b; Lund, Kolta, & Sessle, 2009; Sessle, 2006, 2009; Sessle et al., 2007).

Cortical representation of corticobulbar musculature has been investigated using variety of methods including TMS (Hamdy et al., 1996) and neuroimaging techniques (Grinevich, Brecht, & Osten, 2005; Haque et al., 2010; Hatanaka, Tokuno, Nambu, Inoue, & Takada, 2005; Lund & Kolta, 2006b). Skeletal muscles are represented somatotopically along the motor cortex with the orofacial structures represented laterally and the trunk and limbs represented medially. In addition, most of the orofacial muscles are bilaterally represented in the sensorimotor cortex, whereas most of trunk and limbs muscles have mainly contralateral representation with limited ipsilateral involvement (Grinevich et al., 2005; Haque et al., 2010; Hatanaka et al., 2005; Lund & Kolta, 2006b). M1 activated regularly during the planning, initiation and execution of voluntary corticobulbar tasks (Sessle et al., 2007). Findings from neuroimaging studies support the concept of face M1 involvement in the planning and initiation of orofacial movements given that activation of face M1 in fMRI preceded the onset of EMG activity during jaw movement task (Malandraki et al., 2009; Shibusawa, Takeda, Nakajima, Ishigami, & Sakatani, 2009). The active involvement of M1 in the execution of voluntary conrticobulbar muscles was confirmed by data from animal studies. Providing a short train of intra-cortical micro stimulation (ICMS) to the areas of face M1 was found to trigger orofacial movements such as jaw opening (Avivi-Arber, Lee, Yao, Adachi, & Sessle, 2010b; Burish et al., 2008; Martin et al., 1999; Yao et al., 2002a). In addition, lesions involving face M1 in animals diminished the ability to perform learned voluntary orofacial movements (Hiraba et al., 2007; Yamamura et al., 2002). Reversible cooling of synaptic activity of monkey's face M1 was found to severely affect trained tongue-protrusion task and to a lesser extent a biting task (Hiraba et al., 2007; Murray et al., 1991). In a subsequent study, elemental components of tongue movement were identified in more extensive and more diverse sites in face M1 in monkeys, compared to jaw-closing movement (Murray & Sessle, 1992a, 1992b, 1992c).

Motor neurons along M1 are organized in somatotopic representation in that each area of M1 represents group of muscles that represents anatomical region (Grinevich et al., 2005; Haque et al., 2010; Hatanaka et al., 2005; Lund & Kolta, 2006b). Areas of the orofacial muscles were found to greatly overlap with each other and to a lesser degree with the neighbouring areas that represent the trunk and limbs muscles (Martin et al., 2004). The overlapping between these neural areas have enabled M1 to control coordinated movements that require sequential activation of multiple muscles (Martin et al., 2004). In summary, M1 has been identified to be activated in the execution of voluntary corticobulbar tasks. Findings from neuroimaging studies and animal studies revealed that face M1 plays a role in the planning, initiation and execution of voluntary orofacial movements.

2.1.5.2 ***Role of S1 and sensory feedback in modulating the neural control of corticobulbar tasks:***

S1 receives sensory information from the peripheral sensory receptors, which can consequently modulate the motor plan for corticobulbar tasks at the cortical and brainstem levels by activating or inhibiting motoneurons innervating the orofacial muscles (Grinevich et al., 2005; Haque et al., 2010; Hatanaka et al., 2005; Lund & Kolta, 2006b). Afferents input from chemo, mechano and thermo receptors play an important role in modulating corticobulbar, i.e. M1 to brainstem, excitability (Lund & Kolta, 2006a; Lund et al., 2009; Sessle, 2006, 2009). In fact, dense connections exist not only between S1 and M1, but between S1 and other subcortical areas (Haque et al., 2010; Hatanaka et al., 2005). Interestingly, ICMS to S1 evokes rhythmic orofacial movements, such as jaw movements (Avivi-Arber, Lee, & Sessle, 2010a; Avivi-Arber et al., 2010b; Burish et al., 2008; Martin et al., 1999), underscoring the importance of S1 in human motor control.

In animal studies, S1 has been identified to play a role in the initiation and planning of orofacial movements as some S1 neural activity appeared before the EMG activity at the peripheral muscles (Lin, Murray, & Sessle, 1994a, 1994b; Lin & Sessle, 1994). In fact, suppression of sensory input during performance of orofacial

tasks disrupted the performance of tongue protrusion task (Yao et al., 2002b). A number of studies in human subjects support the findings of the animal studies of the involvement of S1 in the control of orofacial movements. Voluntary as well as naïve orofacial movements have been shown to activate S1 along with other cortical areas such as M1 (Corfield et al., 1999; Ehrsson, Geyer, & Naito, 2003; Foki et al., 2007; Martin et al., 2004; Sörös et al., 2006).

2.1.5.3 ***Asymmetry of cortical control of voluntary corticobulbar movements:***

Cortical input for voluntary corticobulbar movements is uniformly described as bilateral (Kern et al., 2001a; Martin et al., 2004). In fact, most of the orofacial musculature receive bilateral input from the CNS with the exception of the lower part of the face and the genioglossus muscle, which receive only contralateral innervations (Bhatnagar, 2001). Studies revealed that activation of the primary sensorimotor cortex is asymmetric for some orofacial muscles, such as the anterior digastric muscles (Gooden, Ridding, Miles, Nordstrom, & Thompson, 1999; Nordstrom et al., 1999). This asymmetry, however, varies between individuals and tasks (Sowman et al., 2009), suggesting that hemispheric asymmetry must be assessed across individuals and tasks.

Contradictory findings have been reported regarding hemispheric dominancy of the orofacial muscle control. There was no hemispheric dominance for masseter muscle control as evident by similar MEP amplitude following TMS stimulation of right and left hemispheres (Ortu et al., 2008), and the same was found for the mylohyoid muscles (Hamdy et al., 1996). Task related hemispheric dominance was found for the anterior digastric muscle in that at rest and during contraction there was no difference in excitability between hemispheres; however, during speech and jaw movement the left hemisphere had enhanced excitability in comparison the right hemisphere (Sowman et al., 2009). The hemispheric dominance for pharyngeal musculature varied among individuals and tasks (as discussed in section 2.1.4.3) with some showing more lateralization to the right and some to the left, with similar findings for esophageal control (Hamdy et al., 1996).

In summary, most orofacial musculatures receive bilateral innervation from the cortex. Hemispheric dominance was found to be task related and vary across individuals with the exception of the masseter and mylohyoid where no hemispheric dominance was identified during activation of those muscles.

2.1.6 **Neural control of corticospinal tasks:**

Much of our knowledge of human motor control has been established through investigation of the corticospinal motor system. It is well reported that the peripheral system is controlled primarily by the contralateral hemisphere (Springer & Deutch, 1998). Strong contralateral activation of M1 was reported during finger movements using various techniques such as magnetic resonance imaging (MRI), EEG and TMS (Gerloff, Corwell, Chen, Hallett, & Cohen, 1998a; Gerloff et al., 1998b; Gerloff et al., 1997; Kopp, Kunkel, Müller, Mühlnickel, & Flor, 2000; Müller et al., 2000; Pollok et al., 2003; Pollok, Muller, Aschersleben, Schnitzler, & Prinz, 2004). The role of M1 in the execution of corticospinal tasks was confirmed by studies using neurophysiological disruption to M1withTMS or electrical stimulation (Day et al., 1989; Roick, von Giesen, & Benecke, 1993; Rossini, Zarola, Sta°lberg, & Caramia, 1988; Rothwell, Day, Thompson, & Marsden, 1989; Ziemann, Tergau, Netz, & Hömberg, 1997) . Neurophysiological disruption to M1 was found to delay the timing of the movement, but did not affect the pattern of movement suggesting that the motor programme of movement was intact (Day et al., 1989). The delay in the timing of the movement could have been a result of halting transmission of information from the CNS as a result of TMS and electrical stimulation to that area, possibly by mechanisms related to inhibition of the cortical excitability (Day et al., 1989). Neuronal activity would consequently be inhibited and information would not be sent until after recovery from the inhibitory effect, thereby producing a delay. The authors, however, did not identify the area of the target muscles representation in M1; therefor, the origin of the delay was not clearly defined in this study. Absence of focal disruption to the hand muscles representation in M1 might not be sufficient to disrupt the pattern of movement in the previously described study.

Ziemann and colleagues (1997) investigated the origin of delay in timing of movement following TMS stimulation observed in previous studies (Day et al., 1989; Roick et al., 1993; Rossini et al., 1988; Rothwell et al., 1989). Wrist flexion was delayed to a greater extent when TMS was discharged closer to the execution of the motor task. In addition, movement delay increased with increasing TMS intensity. The maximum delay was achieved when TMS stimulation was applied to the area in the M1 that produced the largest muscle twitch in the targeted muscle as well as the longest silent period. The force of the twitch of the targeted muscle has been shown to correlate with the area in M1 that produced consistent MEPs (Hess, Mills, & Murray, 1987). In addition, a positive relationship was identified between the duration of delay in executing the movement and the duration of TMS induced silent period (Wilson, Lockwood, Thickbroom, & Mastaglia, 1993). An increase in the silent period has been shown to correlate with the increase in TMS intensity (Roick et al., 1993). These results collectively indicate that M1 was the origin of delay given the site of stimulation. Ziemann and colleagues concluded that "the delay in timing of the movement is due to an inhibitory process occurring at the final motor output stage" (p. 36). Data from Ziemann et al. further supported the concept that motor plans are stored in a motor-memory in M1 as was suggested by Day et al. (1989). This motor plan is released rapidly by the motor cortex when pre-movement facilitation reached a certain threshold; the application of TMS, however, inhibited the release of this plan. However, the neuronal populations stimulated by TMS may not be limited to the representation of the target muscle in M1; therefore, the delay could be produced by any of the affected neural areas. In fact, subcortical areas such as the basal ganglia have been shown to be activated by the application of TMS over the motor cortex; thus, they may play a role in the observed delay in the timing (Ziemann et al., 1997). The previous studies (Day et al., 1989; Ziemann et al., 1997) did not investigate the possibility of delay in the processing of the auditory cue to produce the movement as a result of the neural disruption. In fact variations in timing of movement were reported in response to different cue modalities, audio or visual signals (Ziemann et al., 1997). The variations in the response to different cue modalities could be a result of the difference in time needed for cognitive processing of the various cues, which is a pre-motor cortex function (Ziemann et al., 1997).

Therefore, one could argue that the delay observed in the above studies could be a result of the delay in processing the external cue rather than delay in the timing of movement itself.

Neural control of the peripheral muscles is not limited to M1. A number of cortical areas have been identified to work collectively with M1to execute corticospinal motor behaviours including SMA, and premotor cortices (Klineberg & Jagger, 2004). The premotor cortices from both hemispheres have been identified to be involved in the execution of corticospinal tasks as strong functional connectivity, referred to as coherence, was evident between M1 and premotor cortices of both hemispheres during finger movement in studies implementing EEG (Gerloff et al., 1998b; Gerloff, Uenishi, & Hallett, 1998c; Manganotti et al., 1998; Serrien, Cassidy, & Brown, 2003; Toma et al., 2002). The fact that EEG recording might be influenced by artifacts of other movements should be taken into account when interpreting data from these studies. The SMA has been identified to play an important role in preparation and initiation of motor movements (Kornhüber & Deecke, 1965). Delayed initiation of sequential finger movements was found when SMA was stimulated using TMS suggesting active contribution of SMA in the planning and initiation of voluntary motor movements (Amassian, Cracco, Maccabee, Bigland-Ritchie, & Cracco, 1991; Amassian, Cracco, & Maccabee, 1990).

2.1.6.1 ***Hemispheric specialization in the control of corticospinal motor behaviours:***

The performance of voluntary corticospinal tasks, such as finger movement during object manipulation, requires high involvement of M1 from the contralateral hemisphere (Caroselli et al., 2006; Kuypers, 1981; Springer & Deutch, 1998). Recent studies, however, revealed that M1 may also play a role in ipislateral motor control, in particular if the movement is complex or requires force to be executed (Callaert et al., 2011; Davare, Duque, Vandermeeren, Thonnard, & Olivier, 2007; Hortobágyi, Taylor, Petersen, Russell, & Gandevia, 2003; Perez & Cohen, 2008; Swinnen & Wenderoth, 2004). Results from neuroimaging studies of a right-handed population

revealed functional hemispheric asymmetry characterized by larger activation of the left hemisphere during left hand movement as compared to right hemisphere activation during right hand movement (Hayashi et al., 2008; Verstynen, Diedrichsen, Albert, Aparicio, & Ivry, 2005). These results suggest that the left hemisphere may play a functional role in the execution of unilateral motor behaviours in the right-handed population (Verstynen et al., 2005). These findings, however, might be due to the recruitment of more neural resources when executing tasks with the non-dominant left hand in right-handed population. Similar results were reported in studies utilizing single pulse TMS to disrupt M1 motor control during a complex finger tapping task in right-handed participants (Chen, Gerloff, Hallett, & Cohen, 1997). Disruption in the timing of finger movement was observed when TMS was applied over the ipsilateral hemisphere, which was particularly evident in left hemispheric interruption. In addition, MEPs were elicited from both hands when high TMS intensities were employed to stimulate M1from both hemispheres (Kagerer, Summers, & Semjen, 2003). This suggests that the MEP was induced through an uncrossed corticospinal pathway in the ipsilateral hand. In fact, direct uncrossed corticospinal fibres have been identified playing a role in controlling ipsilateral movements in animals (Brus-Ramer, Carmel, & Martin, 2009). However, uncrossed corticospinal fibres in human constitute only 10-25% of all descending motor fibres (Nathan, Smith, & Deacon, 1990), suggesting a limited role of these uncrossed pathways in neuromotor control. Kagerer and colleagues further reported that larger ipsilateral MEPs were elicited from the left hand in right-handed participants when left M1 was stimulated as compared to from the right hand when right M1 was stimulated. The above studies recruited right-handed participants only, which hinders the generalization of results to left-handed population. It might be postulated that neural areas from the ipsilateral as well as the contralateral hemispheres are needed when executing tasks with the non-dominant hand.

Van Den Berg, Swinnen, and Wenderoth (2011) recruited both right and left-handed individuals and reported that in right-handed participants disruption to the ipsilateral hand was frequently induced when stimulating the dominant left M1. Left-handed participants, however, showed an interesting phenomena in that only half of

them showed frequent disruption of the ipsilateral hand when the non-dominant left M1 was stimulated. In contrast, the other half of the participants showed more ipsilateral disruption when right dominant M1 was stimulated. These results suggest that handedness as well as hemispheric specialization contributes to the neural control of peripheral movement by M1. It is noteworthy that multiple statistical analyses were performed without correction for type I error, therefore, the results need to be interpreted with caution. Even though it has been identified that the ipsilateral hemisphere might play a role in the execution of corticospinal motor behaviour, it should be emphasized that this contribution is minimal as uncrossed fibres constitute only 10-25% of all descending motor fibres. Therefore, corticospinal motor behaviours are controlled mainly by the contralateral hemisphere with minimal involvement of the ipsilateral hemisphere (Van Den Berg et al., 2011).

Hemispheric asymmetry is not limited to M1 as functional asymmetry has been identified in various parts in the CNS, in particular, parietal and pre-motor areas (Van Den Berg et al., 2011). For example, in right-handed individuals, there is strong activation of the left but not the right superior parietal cortex and dorsal pre-motor cortex during the execution of complex motor tasks (Callaert et al., 2011; Swinnen et al., 2010; Verstynen et al., 2005). These findings suggest that these higher-order areas play a role in modulating M1 involvement in neural control of hand movement. This is particularly evident for the pre-motor cortex as there are dense connections between premotor areas and M1 (Van Den Berg et al., 2011). These studies have focused on the right-handed population. It is unclear whether the same principles apply to the left-handed population.

Summary:

Neural control of corticospinal motor behaviours is well established in that each side of the body is primarily controlled by the contralateral side of the brain. M1 has been identified to play a major role in the execution of voluntary corticospinal tasks as evidenced by results from neuroimaging and neurophysiological studies. Disruption of M1 by TMS or electrical stimulation was found to affect the execution

of corticospinal motor behaviours. Premotor cortices and the SMA were also found to work collectively with M1 to plan and execute corticospinal motor behaviours. The concept of pure contralateral control of corticospinal movement has been challenged as a growing body of evidence supports the likelihood of ipsilateral involvement in the execution of the corticospinal motor tasks. This ipsilateral involvement is observed frequently in the right-handed population and less frequently in the left-handed population. These findings may suggest that handedness as well as hemispheric specialization contribute to the neural control of peripheral movement by M1. The contribution of the ipsilateral hemisphere to the corticospinal movement is minimal given the small portion of uncrossed motor fibres.

2.2. Part B: Methods to investigate neural control and biomechanical changes of motor behaviours:

This section will provide an overview of some of the instrumental measures used to assess neural control and biomechanics of motor behaviours, swallowing in particular, with the focus on instrumentation used in this research programme.

2.2.1 Experimental methods to investigate neurophysiology:

2.2.1.1 *Neuroimaging techniques:*

Neuroimaging techniques, such as MRI and computed tomography (CT), have enabled researchers to observe the extent of lesions produced by brain injury in more details (Pascual-Leone et al., 2000). Combining this knowledge of the brain damaged area with clinical findings and dysfunctions of behaviours have provided insights into the functional contribution of that brain area (Pascual-Leone, Walsh, & Rothwell, 2000). However, neuroplasticity and the possibility that the disruption in the function may be more widespread than anatomical lesion should be taken into account when inferring a causal relationship (Pascual-Leone, Bartres-Faz, & Keenan, 1999).

The emergence of functional brain imaging, such as fMRI and PET, helped to clarify some of the ambiguity surrounding the activation of brain regions in response to motor or cognitive tasks (Pascual-Leone et al., 2000; Sack, 2006).These techniques have enabled researchers to visualize functional patterns and extent of neural activation in response to behavioural tasks (Pascual-Leone et al., 2000; Sack, 2006). For example, the good spatial resolution of the fMRI and PET has enabled researchers to visualize the extent of neural activation during the performance of swallowing tasks (Dziewas et al., 2003), and provided evidence for complex neurophysiological control of swallowing (Malandraki, Johnson, & Robbins, 2011). These neuroimaging techniques have advantages over the electrophysiological techniques in studying brain functions in that it allows investigation of larger areas in the brain with relative ease (Uğurbil, Toth, & Kim, 2003). Further, fMRI provides a

safe non-invasive method to investigate functional neural activation through the ability to detect subtle changes in signals and reliable localization of areas of increased neural activity (Ogawa, Menon, Kim, & Ugurbil, 1998) with 3-5 mm or less spatial resolution (Uğurbil et al., 2003). Despite the good spatial resolution, fMRI and PET have poor temporal resolution which pose a challenge in inferring causal relationships utilizing these techniques alone (Sack, 2006).

Malandraki et al. (2011), identified few limitations of using fMRI technique, in particular in the interpretation of the signals. Investigating neural activation of a task using fMRI requires a comparison task, e.g. "rest" compared to "swallowing". The presence of net difference activation between the two conditions will determine the results; therefore, the fMRI contrast is not quantitative. Furthermore, fMRI is very sensitive to artifacts, such as motion and medications that could affect neural excitability. For example, during the comparison between "swallowing" and "rest" tasks, it is difficult to control for the motor related artifacts caused by swallowing musculature, such as tongue movement not related to swallowing. Additionally, it is hard to quantify the degree of relaxation during the "rest" condition. Due to these limitations other techniques, such as TMS, have been utilized to measure changes in neural excitability during performance of motor behaviours and also to infer causal function relationship.

2.2.1.2 ***Transcranial magnetic stimulation (TMS):***

TMS was first described by Barker, Jalinous, and Freeston (1985) as a non-invasive technique by which to stimulate the motor cortex in humans. Barker et al. (1985) documented the effectiveness of TMS stimulation of the motor cortex because of the ability of the field to pass through high resistance structure. It passes through the skull and scalp virtually unattenuated, and the procedure is painless and non-invasive (Chen, 2000). Thus, TMS has become widely accepted as a non-invasive method to study changes in the motor cortex excitability and to measure changes in central and peripheral conduction times due to cortical and spinal excitability (Darling, Wolf, & Butler, 2006).

To determine corticobulbar or corticospinal excitability and conduction time, TMS of the motor cortex is used to elicit MEPs, measured with electrodes placed on peripheral muscles (Griškova, Höppner, Rukšėnas, & Dapšys, 2006). An electrical impulse is generated by the discharge of a high electrical current through an external coil held parallel to the motor cortex on the scalp. The discharged current induces a transient magnetic field perpendicular to the stimulation coils (Hallett, 2000). The induced magnetic field penetrates through the scalp, skull, and brain tissue. This magnetic field induces a secondary electrical current perpendicular to the magnetic field and parallel, but in the opposite direction, to the primary electrical current in the coil (Epstein, 2008) (Figure 2-3). The secondary electrical current in the underlying neural tissue can, under certain circumstances, facilitates or inhibits excitation of the stimulated neuronal networks (Hallett, 2000; Hallett & Proctor, 1996). The brain tissues including cell bodies, axons, and dendrites are hyperpolarized (increase negativity) at pointes where the current enters and depolarized (decrease negativity) at the point where the current exits (Mills, 1999). A point of stimulation, i.e. depolarization, usually occurs where the current exits the stimulated fibre, typically where the fibre bends across the electrical current or where the electrical current crosses straight fibre (Mills, 1990). If the depolarization exceeds the activation threshold, a propagating action potential will be initiated (Mills, 1990).

The measured MEP is the resulting electrical potential that signifies the muscle's response to the stimulation of the cortical and neuronal pathways (Griškova et al., 2006). The MEP response represents temporal and spatial summation of the descending volleys from the motor cortex to the brainstem (corticobulbar pathway) or to the spinal cord (corticospinal pathway) (Figure 2-3).TMS can be applied with a single stimulus with variation in stimulation intensity, site and orientation of the magnetic field. The muscle response measured as the MEP depends on all these variables and the shape of the stimulating coil (Butler & Wolf, 2003). The response latency of the MEP represents the time from initiation of motor cortex excitation to the first sign of EMG response in the peripheral muscle (Hamdy, Aziz, Rothwell, Hobson, & Thompson, 1998). The amplitude of the MEP represents the level of excitation of the corresponding pathways between the motor cortex and the peripheral

muscle (Chen, 2000). Greater amplitude signifies greater excitation, and a shorter latency implies more efficient transmission of the neural command from the motor cortex to the muscle (Chen, 2000; Misulis, 1994).

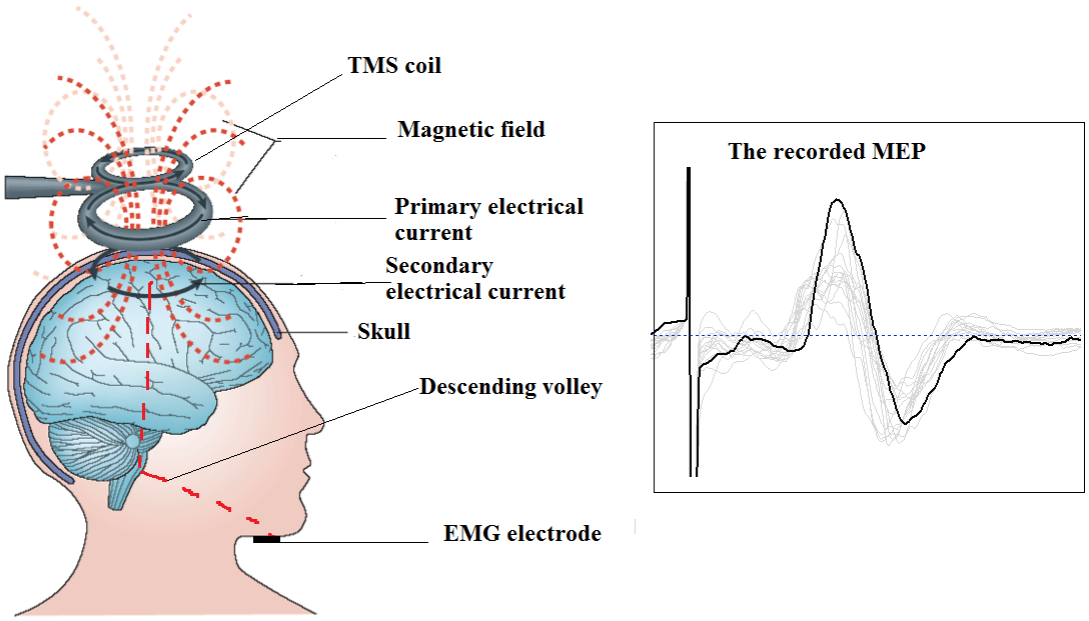

Figure 2-3[3]*: Visual illustration of the primary electrical current (black arrows in the figure of -8 coil) that induces magnetic field (red/ pink dotted lines perpendicular to the coil) which in turn induces a secondary electrical current in the brain (black arrows in the brain). The figure also shows the descending volley from the CNS to the submental muscles group and the recorded MEP response from these muscles.*

In the past two decades, TMS has gained increasing publicity due to its ability to manipulate neural activity to induce non-invasive transient neural disruption in

[3] *Adapted from (Ridding & Rothwell, 2007). Is there a future for therapeutic use of transcranial magnetic stimulation? Nature Reviews Neuroscience, 8(7), 559-567.*

conscious human volunteers. This transient disruption in the neural activity of certain brain areas, which depends on the site of stimulation, enables researchers to observe quantifiable changes in the performance of behaviours. TMS can thus be regarded as a unique research tool for investigating causal structure-function relationship (Pascual-Leone et al., 2000; Sack, 2006). In order to assess functional neuronal network assemblies, various TMS paradigms have been developed, such as single pulse TMS, rTMS, paired pulse TMS, and Theta Burst Stimulation. For the purpose of this discussion, single pulse TMS and rTMS will be reviewed below.

It is important to distinguish between single pulse TMS and rTMS protocols to facilitate understanding of the procedures. The discharge of the magnetic fields is usually time-locked during single pulse procedure, in that TMS stimulus being discharged in unison with certain motor task. Therefore, it is either manually discharged or it can be set to automatically discharge with onset of behavioural task in the event-related stimulation procedure (Sack, 2006). This application of single pulse TMS at different time points during execution of the behavioural task provides an opportunity to investigate the functional contribution of the site of stimulation to the performance of the behaviour (Sack, 2006). In contrast, rTMS can induce longer term modulation in the excitability of the stimulated area even beyond the duration of the stimulation itself (Sack, 2006). This rTMS procedure consists of higher frequency stimulation in the form of pulse trains with rates up to 100 Hz (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000). It was documented that low-frequency rTMS ($\leq$ 1 Hz) tends to inhibit motor cortical excitability whereas higher-frequency rTMS ($\geq$ 5 Hz) tends to increase the excitability of the stimulated area in most individuals (Maeda et al., 2000). Although the application of rTMS can provide modulation of motor cortical excitability that outlasts the stimulation period, there is high intra- and inter-individual response variability (Iyer, Schleper, & Wassermann, 2003; Maeda et al., 2000; Siebner et al., 2004).

For accurate utilization of TMS in investigating causal structure-function relationships, accurate localization of the investigated area in the brain is critical (Sack, 2006). A common approach is the identification of a particular brain area using scalp land marks, for example standard 10-20 electrode scalp positioning

system (Sack, 2006). However, this approach does not account for individual differences between scalp landmarks and underlying areas of the brain or individual differences in functional organization of the brain (Herwig, Satrapi, & Schonfeldt-Lecuona, 2003; Okamoto et al., 2004). Therefore, this approach has been modified and has been used to estimate the location of particular areas of interest, and then the accurate position of that area is identified through inducing consistent high amplitude MEPs from the target peripheral muscles. A potential limitation in utilizing TMS to investigate causal structure-function relationship is the uncertain focal area of the TMS stimulation which is approximately (1 cm^2), which depends on the size of the coil and the stimulation intensity (Sack, 2006). Therefore, it is extremely important to control for accurate coil position, size and intensity when utilizing TMS (Sack, Kohler, Linden, Goebel, & Muckli, 2006).

Previous studies have supported the feasibility of utilizing TMS to investigate neural structure-function relationship in hand (Day et al., 1989; Ziemann et al., 1997), or swallowing muscles (Humbert, 2010; Jefferson et al., 2009; Mistry et al., 2007; Verin et al., 2012). These results were derived from the assumption that TMS-induced behavioural changes are a result of TMS-induced disruption of focal neural activity at the stimulation site (Sack, 2006). However, this might not be the case as some studies revealed that neural disruption induced by TMS may not be restricted to the stimulation site (Bestmann, Baudewig, Siebner, Rothwell, & Frahm, 2005; Denslow, Lomarev, George, & Bohning, 2005; Pleger et al., 2006). This phenomena has been mainly identified through the combination of TMS and functional brain imaging techniques, such as TMS and PET (Paus et al., 1997) and TMS and fMRI (Bohning et al., 1997). A limited number of studies have combined TMS and functional brain imaging techniques to investigate the functional contribution of the primary sensory motor cortex in the execution of motor behaviours. Bestmann, Baudewig, Siebner, Rothwell, and Frahm (2004), utilized high frequency TMS to the hand area on the primary sensory motor cortex while simultaneously measuring neural activity utilizing MRI technique. The authors identified neural changes not only at the site of stimulation, but also changes in other cortical and subcortical structures, albeit to lesser degree. Finger movement have produced similar activation

pattern, therefore the authors suggested that the observed activity reflects the functional connectivity of the stimulated area. The results of this study provided insight to the fact that focal TMS stimulation does not only alter the neural activity of the stimulated area, but also modulates neural activity in remote or inter-connected cortical and subcortical areas. Therefore, the behavioural change could be due to the neural modulation induced to any of the cortical and subcortical areas and could not be fully attributed to the stimulated area. Further investigation is warranted to identify the relationship between the observed behavioural changes and the neural modulation induced by TMS to further strengthen the methods of TMS to investigate causal structure-function relationship (Sack, 2006).

2.2.2 **Behavioural methods to investigate neural control: the dual-task (DT) paradigm:**

A DT paradigm is a non-invasive behavioural method that has been used to assess neural organization (Cherry & Kee, 1991; Hellige & Kee, 1990). In this paradigm participants perform two tasks simultaneously, and an effect in one or both tasks is likely to result if the control of these tasks are closely associated in the CNS (Pashler, 1994). The degree of interference is measured by comparing task performance in isolation to performance in the DT condition (Green & Vaid, 1986). The DT paradigm has a number of advantages over other techniques. It is a non-invasive behavioural task; therefore, it can be performed repeatedly without concern of harm. Furthermore, the DT paradigm requires the performance of the target task, hence testing the functional neural control during the execution of the task. Therefore, cerebral controls and dominance of motor behaviours may be appropriately tested using the DT paradigm.

The DT paradigm has been widely used to assess functional lateralization and hemispheric specialization (Cherry & Kee, 1991; Kinsbourne & Cook, 1971). One of the most frequently used techniques in lateralization research is the concurrent performance of cognitive tasks, linguistic or non-linguistic, during the performance of

manual tasks, such as finger tapping, (Green & Vaid, 1986). The neural control of linguistic tasks, such as naming objects or reading, has been well documented with left hemispheric dominance particularly in right-handed individuals (Kinsbourne & Hicks, 1978). In contrast, non-linguistic tasks such as tracking a line or encoding photographs of faces are lateralized to the right hemisphere (Benton et al., 1975; Warrington & Rabin, 1970). Manual tasks such as a finger tapping have been used in the dual task paradigm because its neural controls are well documented (Springer & Deutch, 1998).

The motor tasks of right and left finger tapping are the most frequently utilized tasks in DT studies investigating cerebral asymmetry (Kinsbourne & Hiscock, 1983). The reliability of these tasks in detecting lateralized effects has been established for different types of finger tapping tasks with different sets of instructions (McFarland & Ashton, 1978a, 1978b, 1978c). Finger tapping tasks such as index finger tapping on single key, index finger tapping on multiple keys, and multiple finger tapping were utilized in different studies. Contradictory findings were identified on the reliability of different finger tapping tasks to detect lateralized effects. With single key tapping utilizing the index finger, subjects are usually instructed to tap as quickly as possible, and their performance is measured by rate and regularity indices (Kee, Morris, Bathurst, & Hellige, 1986). Laterality effects of verbal and visuospatial performance were reliably detected using this motor task procedure (Kee et al., 1986). In addition, Kee, Bathurst, and Hellige (1984) reported less sensitivity of multiple keys finger tapping task to detect laterality. For example Kee et al. (1984) did not detect laterality effects for paragraph reading and Wechsler Intelligence Scale for Children block design solution when each of these tasks was paired with manual task required a sequential tapping of two or three keys. However, reliable left-and right-hemisphere laterality effects were observed when the single key tapping method was utilized. Kee et al. (1986) suggested that the use of single key tapping procedure was more reliable for two reasons. Firstly, complexity of alternating the tapping of two keys might require a lengthy practice period in order to be adequately performed, thus the limited practice of this alternating movement may mask the interference effects. On this note, single key tapping task has been shown to

reliably detect lateralized interference in the absence of lengthy practice. Secondly, the simple task of single key tapping is less affected by factors such as spatial accuracy and force modulation. Therefore, the repetitive tapping of index finger on single key is viewed as the method of choice in DT studies utilizing finger tapping.

Various measures of manual performance were utilized in finger tapping procedures, such as rate and regularity of finger tapping. It was suggested that rate and regularity measures provide similar estimates of lateralized interference when the verbal task is concurrently performed with finger tapping (McFarland & Ashton, 1978a). However, a review by Kinsbourne and Hiscock (1983) provided evidence that rate and regularity measures produced different estimates of lateralized interference. Therefore, testing rate and regularity could reveal stronger evidence of lateralized interference rather than utilizing just one of these measures.

2.2.2.1 ***Theories underlying the effect of DT paradigm on functional infrastructure:***

Performing more than one task concurrently may result in interference in the functional infrastructure due to limitations in neural system and competition for cognitive processing, capacity, attention or neural resources (Caroselli et al., 2006; Kahneman, 1973; Norman & Bobrow, 1975). A number of theories have been proposed to explain the phenomena of the DT paradigm; however, the most accepted theories are "functional cerebral distance" (Kinsbourne & Hicks, 1978) and "capacity sharing" (Kinsbourne & Hiscock, 1983).

Kinsbourne and Hicks (1978) introduced the "functional cerebral distance" model to interpret the results of the DT paradigm. According to this model, each neuronal area in the brain is specialized for a particular function and there is a connection between the areas in the brain, in particular areas within the same hemisphere. Thus, when two tasks activate interconnected areas within the same hemisphere, a greater disruption is expected than when performing two tasks activating areas in different hemispheres as those areas overlap to a lesser degree

(Kinsbourne & Hicks, 1978). In other words, interference in one or both tasks could be expected as a result of sharing functionally related cerebral infrastructure (Kinsbourne & Hiscock, 1983; Klingberg & Roland, 1997). For example, primarily left-hemispheric task of speaking disrupts the performance of right finger movement, which is primarily controlled by the motor areas of left hemisphere (Kinsbourne & Cook, 1971). According to the functional cerebral space theory the magnitude of interference between two tasks depends on the level of neuronal connection between the neural areas controlling the tasks (Caroselli et al., 2006). Therefore, more interference could be expected if the two tasks used resources from the same hemisphere in contrast to tasks utilizing different hemispheres (Caroselli et al., 2006).

The "capacity sharing" theory describes the effect of DT interference as a result of sharing mental resources, or processing capacity among tasks (Kinsbourne & Hiscock, 1983; Klingberg & Roland, 1997; Pashler, 1994). Therefore, when performing two tasks concurrently, there will be less capacity to process each task, which would result in impairment in the performance of one or both tasks (Pashler, 1994). The **"**capacity sharing" theory is based on the idea that for certain mental operations, the human system does not have the ability to process more than one task at a given time; therefore, some complex mental operations would require greater resources and mechanisms than others (Pashler, 1994). Thus, the concurrent performance of two tasks would require processing at the same time; therefore, this would result in impairment or delay in one or both of these tasks. For example, the concurrent performance of finger tapping and speaking would require concurrent processing. According to the capacity sharing theory, there will be less capacity to process both of these tasks at the same time, hence the effect in performance in one or both tasks.

2.2.2.2 ***Theories underlying the demand in attention during DT paradigm***

Greater attentional demand is required when performing two tasks concurrently than when performing each task in isolation (Green & Vaid, 1986). A number of theories have been proposed to address the demand in attention during the

DT paradigm. Welford (1959) proposed the "single channel theory" which regards the human nervous system as a single pool processing resources; therefore, attention cannot be divided across tasks when performed concurrently. This theory suggests the switching of attention from one task to the other during the concurrent performance of two tasks, hence the deterioration of performance in one or both tasks. This theory has been challenged by the fact that humans are able to perform some tasks concurrently without observable effects, such as walking and talking, or driving and talking. In contrast to the "single channel theory", Navon and Gopher (1979) proposed the "multiple channel theory" which proposes that the system has multiple channels to process concurrent tasks; therefore, attention can be shared between tasks. This theory is supported by the lack of interference during the performance of two automatic tasks such as walking and talking, however, it has been challenged by the observable effects during the performance of higher demanding tasks such as finger tapping and swallowing (Daniels et al., 2002; Daniels et al., 2006). The discrepancies in the previous theories have led Kahneman (1973) to propose an intermediate theory with the notion of "limited capacity processing system". This theory is the most accepted theory and indicates that attention can be shared between tasks when performed concurrently; however, greater attentional capacity is required during the performance of dual tasks in comparison to the performance of single tasks.

2.2.2.3 ***Factors influencing DT paradigm results:***

Hemispheric specialization versus manual dominance:

Previous research utilizing the DT paradigm revealed asymmetrical interference in finger tapping performance when paired with linguistic tasks compared to tapping in isolation (Kinsbourne & Hiscock, 1983). Specifically, tapping with the right hand which is controlled by the left hemisphere showed greater disruption than the left hand during concurrent performance with linguistic tasks which are lateralized to the left hemisphere (Hellige & Kee, 1990; Kinsbourne &

Hiscock, 1983). This DT interference was found to be reliable in right-handed subjects (Clark, Guitar, & Hoffman, 1985), and it is more sensitive in identifying hemispheric lateralization for language than handedness (McFarland & Geffen, 1982). A consistent pattern of interference was observed in right-handed participants when concurrently performing linguistic and manual tasks; however, this was not the case for left-handed individuals (Hiscock, Kinsbourne, & Green, 1990). Studies investigated right and left-handed subjects have revealed interesting results regarding hemispheric specialization versus manual dominance during DT paradigm. Studies pairing finger tapping with verbal production tasks revealed either symmetrical pattern of interference for left-handed individuals (Sussman, 1982), or asymmetrical dominant hand interference. Left-handed individuals showed greater reduction in tapping with left hand while individuals who were right-handed showed greater reduction in tapping with right hand during concurrent performance with verbal production task (Orsini, Satz, Soper, & Light, 1985; Simon & Sussman, 1987; Van Strien & Bouma, 1988).

It is well documented that speech production is localized to the left hemisphere in the majority of right handed-individuals, and in about 60-70% of left-handed individuals (Rasmussen & Milner, 1975; Segalowitz & Bryden, 1983). Therefore, one would expect a greater disruption during right hand tapping when performed with verbal production tasks in most left-handed individuals (Caroselli et al., 2006). However, this was not evident as greater disruption was identified during left hand tapping in left-handed individuals indicating that manual dominance could play a role in the interference pattern during DT paradigm (Caroselli et al., 2006; Orsini et al., 1985; Simon & Sussman, 1987; Van Strien & Bouma, 1988). In contrast, Cherry and Kee (1991) found that the manual dominance effect was less pronounced or even absent for subjects who had manual and auditory dominance on opposite sides. Therefore, hemispheric specialization plays a role in influencing the extent of interference in DT paradigm. These findings indicate that hemispheric specialization as well as manual dominance play a role in manual interference. Therefore, separating these effects will give a clearer idea about the level of contribution of each factor in the extent of interference during DT paradigm.

Tapping rate:

Tapping rate has also been identified to affect the level of interference during DT studies. That is, fast tappers with a dominant hand, left or right, exhibit the strongest right or left lateralized effect for verbal production tasks (Steiner, Green, & White, 1992; Sussman, 1989). Positive association has been identified between the tapping rate of the dominant hand and the magnitude of interference (Sussman, 1989). A great effect was identified on the tapping rate of faster tappers than slower tappers during the concurrent performance of finger tapping and verbal production (Simon & Sussman, 1987; Sussman, 1989). Thus, the magnitude of interference of the dominant hand performance was positively associated with the level of lateralized effect in the contralateral hemisphere of the dominant hand (Sussman, 1989). These studies, however, did not control for the possibility of divided attentional demands between the tasks nor vary the tasks complexity; therefore, these factors should be considered when drawing conclusions from these studies.

Divided attentional demands between tasks:

The lateralized effect during concurrent performance of two tasks in a cognitive-manual design could be the result of the manual task or the cognitive task. For example, in language-manual design of DT, if the language task consists of performing a routinized skill that requires a low level of attention, such as reading aloud, attention could be diverted to the manual task and the effect could be a representation of the motor component (Steiner et al., 1992). However, it is difficult to quantify the attentional demand needed for each task. Therefore, when pairing two tasks during a DT paradigm, it is important to manipulate the complexity of the manual tasks and/or manipulate the attentional level required for the cognitive tasks to identify the source of lateralized effect. Hellige and Longstreth (1981) conducted a language- manual design DT study where subjects either read silently or loudly, with or without paying attention to the meaning and the content of the words. Results

showed no significant differences between hands in tapping disruption when low attention was required during the silent reading without paying attention to the content. There was, however, an asymmetrical effect when participants were asked to vocalize the words. Furthermore, when subjects were asked to pay attention to the content of the words, asymmetric interference was present with silent and aloud reading conditions. The authors reported that as the cognitive demands increase, more resources are needed thus more disruption could be seen in the manual task.

In order to accurately measure the lateralized effects during the concurrent performance of two tasks in DT paradigm, the effects of each task on the concurrently performed task should be measured (Caroselli, Hiscock, & Roebuck, 1997). The effects between tasks were neglected in most studies utilizing cognitive-manual design in DT paradigm due to the inability to measure the performance of cognitive tasks, or decreased sensitivity of the cognitive tasks (ceiling effect) (Caroselli et al., 2006). Therefore, in order test the effect of each task on the concurrently performed task in the DT paradigm, both tasks should be measurable and manipulation of tasks complexity should be considered to increase the sensitivity of the tasks.

Summary:

The investigation of neural control of motor behaviours became more precise with the emergence of functional brain imaging techniques. These techniques such as fMRI and PET have good spatial resolution which enabled researchers to visualize the extent of activation during the performance of motor behaviours; however, the poor temporal resolution of these techniques has obstructed the establishment of causal structure-function relationships. Recently, TMS has gained increasing use as a tool of measuring causal structure-function relationship due to its ability to manipulate neural activity and consequently observe quantifiable changes in the performance of behaviours. In addition to instrumental methods, behavioural methods have also been used to investigate neural organization during motor behaviours. The DT paradigm is one of the most common behavioural techniques. DT is a non-

invasive behavioural assessment technique and can therefore, be repeated more often without concern of harm. However, this is a fairly new technique and more in depth investigation is needed to verify the results seen from studies using this technique in the area of swallowing in particular.

2.2.3 **Methods to investigate biomechanics of swallowing:**

2.2.3.1 ***Imaging techniques:***

A number of techniques have been utilized to investigate the biomechanics of swallowing. The most popular technique is VFSS also referred to as the "gold standard" in swallowing evaluation (Rugiu, 2007). VFSS enables the evaluation of all phases of swallowing in a two-dimensional dynamic view making it the tool of choice for assessing the biomechanics of swallowing. Fibreoptic endoscopic evaluation of swallowing (FEES) is another commonly used tool to assess the swallowing function. FEES provides direct view of the larynx in three-dimensional dynamic images enabling the assessment to the pharyngeal phase of swallowing in particular assessment of airway protection mechanisms prior and post swallowing (Langmore, Schatz, & Olsen, 1988). One of the main limitations of FEES is that it does not allow visualization of the majority of swallowing dynamics during swallowing due to obliteration of the image at the peak of pharyngeal swallowing (Langmore et al., 1988). This obliteration of the image is caused by the reflection of the light back to the camera from the swallowing structures.

The interpretations of results from VFSS and FEES in clinical settings are based mainly on subjective and qualitative descriptions as quantifying specific swallowing components such as level of hyoid movement requires complex data calibration and transformation. Therefore, the utility of these tools in research is limited due to the complexity of objective interpretation of the results. In addition, the limitation of visualizing biomechanics events in FEES and the radiation exposure in VFSS pose further challenges in using these tools in research investigating healthy population in particular.

2.2.3.2 ***Pharyngeal manometry:***

Pharyngeal manometry is a technique used to measure the pressure generated by the pharyngeal muscles during swallowing. In contrast to VFSS and FEES, pharyngeal manometry allows assessment of swallowing function by inference from pressure measures obtained at various levels in the pharynx during swallowing. Pharyngeal manometry involves placing a catheter transnasally into the pharynx and to the level of UES. The manometry catheter usually houses three (Butler et al., 2009; Gumbley, Huckabee, Doeltgen, Witte, & Moran, 2008) or four sensors (McConnel et al., 1988). Solid-state sensors allow measurement of the amplitude and timing of pressure generation in the upper-pharynx, mid-pharynx, and UES during swallowing (Dodds, 1987; Salassa, DeVault, & McConnel, 1998).

In order to better understand manometric data related to swallowing, researchers paired this technique with VFSS to correlate pressure data with biomechanical events (Brasseur & Dodds, 1991; Cook et al., 1989; Kahrilas & Shi, 1998; Olsson et al., 1995; Pauloski et al., 2009). The appearance of the "M-wave" at the level of the UES has been linked to rise of contracted UES during hyolaryngeal excursion followed by drop in pressure during the relaxation of the UES and the pressure rise again as UES returns to state of tonic contraction (Castell & Castell, 1993). The M-wave has been used as a marker for accurate catheter placement in number of studies utilizing pharyngeal manometry in isolation (Gumbley et al., 2008; Huckabee, Butler, Barclay, & Jit, 2005; Huckabee & Steele, 2006; Witte et al., 2008). The accuracy of manomertic catheter placement is standardized by using the appearance of M-wave in the UES sensor; however, the anatomy of the pharynx varies between individuals which consequently can lead to slight variation in the location of upper pharyngeal and middle pharyngeal sensors across individuals. This can produce a limitation in comparing data across individuals (Butler et al., 2009). Therefore, within-subject comparison may assist in minimizing the limitation of variation in sensors location between individuals.

Pairing manometry with VFSS (manofluorography) can assist in eliminating the issue of sensors direction (Olsson et al., 1995) and, therefore, enhance the accuracy of interpreting manometric data. Manofluorography can also assist in differentiating between two types of pressure recorded during swallowing: contact pressure and intra-bolus pressure. Contact pressure is the pressure generated by the pharyngeal wall during swallowing, and intra-bolus pressure is the pressure within the bolus that is recorded when the bolus passes over the sensor (Brasseur & Dodds, 1991). Without concurrent VFSS, it is almost impossible to measure intra-bolus pressure due to inability to identify the location of the bolus around the sensor. However, using manofluorography technique requires radiation exposure which could pose a challenge in justifying the use of the technique when investigating healthy populations.

Manometric measures could be influenced by a number of factors including the diameter and shape of the catheter as well as the position and size of the sensors (Brasseur & Dodds, 1991; Dodds, 1987; Lydon et al., 1975). Larger catheters are usually required to house circumferential sensors compared to smaller catheters that house unidirectional sensors. Circumferential sensors may be more sensitive in recording pressure in the pharynx than unidirectional sensors; however, increased catheter size has been associated with larger variation in manometric recordings (Lydon et al., 1975; Olsson et al., 1995; Wilson et al., 1989). Larger catheters have also been reported to influence the bolus flow in the pharynx (Brasseur & Dodds, 1991). Therefore, using smaller catheters that house unidirectional sensors may minimize the above mentioned issues and provide more representative data of pharyngeal pressure during swallowing. Recording asymmetric pressure could be one of the concerns when using unidirectional sensors. However, using an ovoid catheter allows maintenance of the sensors in a given direction to ensure pressure is recorded from the same direction during swallowing (Castell & Castell, 1993; Salassa et al., 1998). Therefore, ensuring constant catheter orientation can eliminate variance introduced by radial pressure.

2.2.3.3 ***Electroencephalography (EMG):***

EMG is a technique used to record electrical muscle activity (Perlman, Palmer, McCulloch, & Vandaele, 1999). EMG has been used to quantify the degree of muscle contraction, identify the temporal features of muscle contraction, monitor muscle performance and fatigue and identify muscle abnormalities (Dideriksen, Farina, & Enoka, 2010; Huckabee et al., 2005; Huckabee & Steele, 2006; Mills, 2005). Two types of EMG have been used in clinical and research settings: intramuscular EMG and surface EMG. Intramuscular EMG consists of insertion of needle electrodes into the muscle of interest. It is used particularly when testing individual muscle, therefore the recording of intramuscular electrodes is restricted to very small space (Mills, 2005; Palmer, Luschei, Jaffe, & McCulloch, 1999). Surface EMG on the other hand is less invasive than intramuscular EMG. It involves placing electrodes over the skin surface overlying the target muscles (Crary & Groher, 2000). Surface EMG allows the recording of combined activity of a number of muscles underneath the electrodes providing approximate values of the collective electrical activity of muscles. Specific to swallowing, surface EMG is favoured technique when measuring activity of submental muscle group during swallowing (Palmer et al., 1999). Surface EMG provides a picture of muscle activation during functional tasks making it a tool of choice in both clinical and research settings (Crary & Groher, 2000). Surface EMG has been implemented in studies investigating swallowing biomechanics, particularly those evaluating the submental muscle group, as well as using it as a form of biofeedback for dysphagia rehabilitation (Crary, Carnaby Mann, Groher, & Helseth, 2004; Huckabee & Cannito, 1999). However, the distance between surface EMG electrodes and target muscles vary across individuals due to skin and subcutaneous tissue thickness. This can produce a limitation in comparing data across individuals. Therefore, within-subject comparison should be considered when interpreting EMG data.

Summary:

Biomechanics of swallowing have been investigated using a variety of tools, with the "gold standard" being the VFSS, which enables the visualization of phases of swallowing in a two-dimensional dynamic image. However, the associated radiation exposure occurring with this evaluation makes it difficult to use in research with healthy adults. FEES is another imaging technique that is used clinically and provides a three-dimensional dynamic image of pharyngeal phase of swallowing. The limitation of visualizing bio-mechanical events of swallowing is one of the major limitations of using FEESS in research settings. Pharyngeal manometry is the only tool to measure pressure generation in the pharynx during swallowing. Ensuring accurate placement of manometry catheter is one of the most important considerations when using this technique. Surface EMG in non-invasive tool used in research and clinical settings to investigate muscle activity. Therefore, it is favoured over other invasive techniques to measure the degree and temporal characteristics of muscle activation during the performance of motor behaviours.

2.3. **Summary, limitations and future directions:**

Swallowing is a complex sensorimotor task that requires a precise coordination of 32 pairs of muscles controlled by independent CNs and combination of cranial and spinal nerves. The complexity of swallowing behaviour is derived from its complex neural control, which includes input from various sources including swallowing regions in the cerebral cortex and brainstem. Results from studies employing a number of neurophysiological assessments suggest a contribution of neural cortical networks to the planning, initiation and possibly the execution of swallowing. In addition studies implanting neuroimaging studies identified neural activation in multiple cortical areas, particularly in M1 and S1, during the performance of volitional swallowing and swallowing related motor tasks. This neural activation suggests possible involvement of M1 and S1 in the regulation of volitional swallowing and swallowing related motor tasks. More medial activation

was observed during reflexive swallowing tasks compared to volitional swallowing tasks suggesting possible involvement of M1 and S1 in the control of reflexive swallowing. The functional contribution of each neural area in regulating swallowing is not clearly understood in particular the role of M1 in the reflexive pharyngeal swallowing is not clearly defined.

The role of M1 in pharyngeal swallowing has recently been investigated. Contradictory findings have been reported regarding M1 contribution in regulating pharyngeal swallowing. A number of researchers have concluded that M1 may play a role in regulating swallowing related motor tasks with the rest of the swallowing process controlled by the CPG in the brainstem. In contrast, studies utilizing neurophysiological disruption mechanisms to the pharyngeal muscles representation on M1 identified a role of M1 in regulating the initiation of pharyngeal swallowing. However, no studies investigated the effect of neurophysiological disruption on the biomechanical events of pharyngeal swallowing. Given the above contradictory findings, further studies are warranted to clarify the role of M1 in the biomechanics of pharyngeal swallowing.

In addition to the experimental methods, a behavioural method, the DT paradigm, has also been utilized to investigate neural organization during swallowing. Results from studies implementing this method suggested bilateral representation of swallowing with different roles of each hemisphere in the regulation of swallowing process. However, a number of methodological limitations have been identified in those studies. These limitations included the utilization of non-quantifiable tasks, e.g. silent word repetitions, which hinders testing the effect of each tasks on the other concurrently performed task. Therefore, further studies utilizing quantifiable tasks and objective outcome measures, such as VFSS or pharyngeal manometry, are warranted to clarify the effect of neural disruption utilizing the behavioural method of DT paradigm on swallowing biomechanics.

Discreet water or saliva swallowing has been utilizing to test swallowing function in most studies investigating the neural control or the biomechanical events of swallowing. However, normal people complete multiple consecutive swallows

during liquids ingestion. Biomechanical differences between discrete and continuous swallowing have been identified in studies implementing VFSS. However, quantitative data regarding pharyngeal sequencing and pharyngeal pressure generation mechanisms during swallowing cannot be inferred from VFSS. Pharyngeal manometry is the method of choice to investigate pharyngeal pressure generation mechanisms. It offers excellent temporal resolution providing quantitative data about the pharyngeal and UES pressure generation mechanisms during swallowing. Further studies are needed to investigate the biomechanical differences between discrete and continuous swallowing to provide further understanding in this area.

Chapter 3: **Hypotheses**

3.1. **Hypotheses**

The following hypotheses were tested in this research programme.

3.1.1 **The effect of trials on the performance of corticospinal and corticobulbar motor behaviours. (Chapter 5)**

Question: Performing multiple trials of a motor task may result in change in performance due to factors such as practice or fatigue. This trial effect may confound interpretation of experimental results. To ascertain the effect of trial execution on the outcome measures used in this research, the following question was investigated. Does performing multiple trials of motor tasks result in significant changes in performance of the targeted corticospinal and corticobulbar tasks used in this research?

Hypothesis 1 A: Performing multiple trials of the voluntary corticospinal task of finger movement will result in significant increase in the regularity and rate of finger movement as measured by a finger tapping device.

Hypothesis 1 B: Performing multiple trials of the voluntary corticobulbar task of jaw movement will result in significant increase in the regularity and rate of jaw movement as measured by EMG.

Hypothesis 1 C: Performing multiple trials of the voluntary corticobulbar task of eyebrow movement will result in significant increase in the regularity and rate of eyebrow movement as measured by EMG.

Hypothesis 1D: Performing multiple trials of the voluntary task of volitional continuous swallowing will result in significant increase in rate, regularity, and volume of liquid ingested per swallow but not pharyngeal pressure generation as measured by pharyngeal manometry.

Hypothesis 1 E: Performing multiple trials of reflexive continuous swallowing will result in no significant change in rate, regularity, or volume of liquid ingested per swallow and no change in pharyngeal pressure as measured by pharyngeal manometry.

Justification: Most healthy subjects have the ability to learn new skills or improve existing skills given the opportunity to practice (Lee, Hinder, Gandevia, & Carroll, 2010). Post-training improvement in corticospinal behaviours, such as sequential finger tapping, has been reported in the trained limb (Parlow & Dewey, 1991). Furthermore, it has been reported that repetition of corticospinal tasks such as thumb abduction has altered the cortical excitability as evidenced by increased MEP amplitude recoded from the extensor pollicis brevis muscle (Bütefisch et al., 2000). Repetition of tasks has also been reported to alter cortical excitability of the corticobulbar musculature measured by increased MEP amplitude in response to repeated water swallows (Fraser et al., 2003). However, it is not clear if the change in cortical excitability is functionally relevant. M1 has been identified to play an important role in regulating volitional swallowing tasks with reduced involvement of M1 in regulating pharyngeal swallowing. This is particularly true for reflexively initiated swallows which bypass the oral phase (Doeltgen et al., 2011; Huckabee et al., 2003; Kern et al., 2001a; Kern et al., 2001b; Martin et al., 2004). Based on the existing research, repetitions of swallowing tasks may yield a change in cortical excitability of M1 and; therefore, affect the behavioural measurements of volitional but not the reflexive continuous swallowing. Furthermore, no change would be expected of repetitions of swallowing tasks on pharyngeal pressure generation that are thought to be heavily controlled by the brainstem.

Significance: A baseline study allows the effect of factors such as fatigue and practice to be estimated and considered in the experimental data, thereby increasing power.

Study design: Participants were asked to perform five blocks of trials of each task in randomized order. Each task was continuously executed for 7 sec, as quickly and regularly as possible. The rate and regularity of the tested measures were

recorded and compared across the five blocks of trials. For swallowing tasks, the volume ingested per swallow and pharyngeal pressures were compared across the blocks of trials.

3.1.2 **The effect of dual-task interference on pharyngeal swallowing. (Chapter 6)**

Question: Volitional continuous swallowing has been tested in prior studies utilizing a DT paradigm to investigate swallowing lateralization (Daniels et al., 2002; Daniels et al., 2006). However, no studies have investigated the effect of DT on reflexively- initiated swallowing. In addition, a DT paradigm that pairs motor tasks which utilize different motor pathways (corticospinal vs corticobulbar) may not explicitly challenge the neural interference created by these tasks. Therefore, the following questions were investigated: Does reflexive, continuous swallowing yield different results to volitional continuous swallowing when concurrently performed with another motor task? Would pairing two tasks that utilize similar motor neural pathways yield different results as compared to pairing two tasks that utilize different motor neural pathways?

Hypothesis 2 A: The performance of concurrent finger tapping during volitional continuous water swallowing will result in:

- Reduced rate of swallowing when compared to baseline as measured by the number of swallows executed in 7 sec using pharyngeal manometry.
- Reduced volume of water ingested per swallow when compared to baseline as measured by average volume per swallow completed in 7 sec.
- No significant change in the amplitude and duration of pharyngeal pressure as measured by pharyngeal manometry.
- Increased irregularity of finger tapping in 7 sec when compared to baseline results measured by the consistency of the inter-movements intervals using a finger tapping device.

- Reduced number of finger taps when compared to baseline as measured by number of taps completed in 7 sec using a finger tapping device.

Hypothesis 2 B: The performance of concurrent finger tapping task during reflexive continuous swallowing will result in:

- No significant reduction in rate of swallowing when compared to baseline as measured by the number of swallows executed in 7 sec using pharyngeal manometry.
- No significant reduction in volume of water ingested per swallow when compared to baseline as measured by average volume per swallow completed in 7 sec.
- No significant change in the amplitude and duration of pharyngeal pressure as measured by pharyngeal manometry.
- No significant change in regularity of finger tapping in 7 sec when compared to baseline results measured consistency of the inter-movements intervals using a finger tapping device.
- No significant change in number of finger taps when compared to baseline results as measured by the number of taps completed in 7 sec using a finger tapping device.

Hypothesis 2 C: The performance of concurrent finger tapping task during continuous eyebrow movement will result in:

- Reduced rate of eyebrow movement when compared to baseline as measured by the number of movements executed in 7 sec using EMG.
- Increased irregularity of eyebrow movement in 7 sec when compared to baseline results as measured by consistency of the inter-movement intervals using EMG.
- Increased irregularity of finger tapping in 7 sec when compared to baseline results measured consistency of the inter-movement intervals using a finger tapping device.

- Reduced number of finger taps when compared to baseline results as measured by the number of taps completed in 7 sec using a finger tapping device.

Hypothesis 2 D: The performance of concurrent eyebrow movement during volitional continuous water swallowing will result in:

- Reduced rate of swallowing when compared to baseline as measured by the number of swallows executed in 7 sec using pharyngeal manometry.
- Reduced volume of water ingested per swallow when compared to baseline as measured by average volume per swallow completed in 7 sec.
- No significant change in the amplitude and duration of pharyngeal pressure as measured by pharyngeal manometry.
- Increased irregularity of eyebrow movement in 7 sec when compared to baseline results as measured by the consistency of the inter-movement intervals using EMG.
- Reduced the number of eyebrow movements when compared to baseline results as measured by number of eyebrow movement completed in 7 sec using EMG.

Hypothesis 2 E: The performance of concurrent eyebrow movement during reflexive continuous water swallowing will result in:

- No reduction in rate of swallowing when compared to baseline as measured by the number of swallows executed in 7 sec using pharyngeal manometry.
- No reduction in volume of water ingested per swallow when compared to baseline as measured by average volume per swallow completed in 7 sec.
- No significant change in the amplitude and duration of pharyngeal pressure as measured by pharyngeal manometry.
- No change in irregularity of eyebrow movement in 7 sec when compared to baseline results as measured by consistency of the inter-movement interval using EMG.

- No reduction in number of eyebrow movements when compared to baseline results as measured by number of EMG peaks produced in 7 sec.

Justification: M1 has been identified to play a major role in the execution of voluntary corticospinal tasks (Caroselli et al., 2006; Springer & Deutch, 1998), as well as self-initiated voluntary corticobulbar tasks (Avivi-Arber et al., 2011; Kern et al., 2001a; Martin et al., 2004; Sessle, 2009). In addition, it has also been suggested that M1 plays important role in regulating volitional swallowing related tasks with reduced involvement of M1 in regulating pharyngeal swallowing, in particular if swallowing bypasses the oral phase (Doeltgen et al., 2011; Huckabee et al., 2003; Kern et al., 2001a; Kern et al., 2001b; Martin et al., 2004). Therefore, pairing tasks that share neural resources from M1- volitional swallowing, finger tapping, and eyebrow movements - might yield a change in the performance in one or both of the tasks as reported in the previous studies utilizing DT paradigm (Daniels et al., 2002; Daniels et al., 2006). In contrast, pairing tasks that utilize neural resources from distinct areas in the brain may not result in significant effects on either task when they performed concurrently. Therefore, pharyngeal pressure generation mechanisms might not be affected when volitionally or reflexively initiated swallowing is paired with other motor tasks.

Significance: This project will help to clarify the role of M1 in swallowing, therefore, extending the current knowledge of swallowing neurophysiology. Furthermore, this project will expand application of the DT paradigm in swallowing research by pairing swallowing with another motor task that utilizes the same, corticobulbar neural pathways.

Study Design: A DT paradigm was used to disrupt the neural commands from the brain to the target muscles during the performance of motor tasks. Swallowing was paired with a motor task, finger tapping and eyebrow movement, which activate brain regions controlling voluntary motor behaviour. If swallowing engages the same cortical region or neural pathway, the tasks are expected to be performed more poorly when performed together.

3.1.3 **The effect of electrophysiological disruption to corticobulbar pathways on pharyngeal swallowing. (Chapter 7)**

Question: The functional contribution of M1 in the execution of voluntary corticospinal and corticobulbar tasks is well documented in the literature. Swallowing, however, has both voluntary and reflexive components. Therefore, it is unclear if M1 has active involvement in the more reflexive components of swallowing: the pharyngeal swallowing. No studies have thoroughly investigated the possible contribution of M1 in regulating the coordinated movement of pharyngeal musculature during swallowing using pharyngeal manometry. The following questions will be investigated: Does creating electrophysiological disruption to the M1 representations of muscles associated with swallowing yield observable changes in the pharyngeal pressure generation of the swallowing tasks? In addition, does creating electrophysiological disruption to the M1representations of muscles associated with voluntary corticospinal and corticobulbar tasks yield observable changes in the performance of those tasks?

Hypotheses 3: Electrophysiological disruption of the dominant and non-dominant motor cortex associated with volitional continuous swallowing will result in:

- No significant change in pharyngeal pressure when compared to baseline as measured by pharyngeal manometry.
- Reduced rate of swallowing when compared to baseline as measured by the number of swallows executed in 7 sec using pharyngeal manometry.
- Reduced volume of water ingested per swallow when compared to baseline as measured by average volume per swallow completed in 7 sec.
- Increased irregularity of volitional swallowing when compared to baseline as measured by the consistency of the inter-swallow intervals using pharyngeal manometry.

Justification: Based on the previous literature, involvement of M1 in the oral phase of swallowing is clear with active contribution to control of voluntary

movement of the swallowing musculature (Kern et al., 2001a; Martin et al., 2004). Providing an external stimulus during the execution of volitional continuous swallowing, such as TMS, should disrupt initiation of the internally generated motor command if it utilizes the same neural pathway. Therefore, disruption of the oral phase during volitional ingestion of liquid may result in disruption of the voluntary components of the tightly controlled sequence of swallowing and consequently induce observable behavioural changes. This disruption may also disrupt the timing of the initiation of swallowing (Humbert, 2010; Jefferson et al., 2009; Mistry et al., 2007; Verin et al., 2012); however, the level of contraction and the sequence of the pharyngeal musculature might not be affected due to reduced involvement of M1 (Jean, 2001). Bilateral activation of M1 has been reported during swallowing tasks; however, some studies reported hemispheric lateralization during different phases of swallowing in that volitional swallowing was more lateralized to the left hemisphere compared to reflexive swallowing (Furlong et al., 2004; Martin et al., 2004; Michou & Hamdy, 2009). Bilateral representation of pharyngeal and esophageal areas in the primary motor cortex has been well documented with functional hemispheric dominance independent of handedness (Hamdy et al., 1996). Therefore, stimulating either hemisphere may produce significant effects due to the bilateral involvement during the execution of swallowing.

Hypotheses 4: Electrophysiological disruption of the dominant and non-dominant motor cortex associated with reflexive continuous swallowing will result in:

- No significant change in pharyngeal pressure when compared to baseline as measured by pharyngeal manometry.
- No significant reduction in rate of swallowing when compared to baseline as measured by the number of swallows executed in 7 sec using pharyngeal manometry.
- No significant reduction in volume of water ingested per swallow when compared to baseline as measured average volume per swallow completed in 7 sec.

- No significant change in regularity of reflexive swallowing when compared to baseline, as measured by the consistency of the inter-swallow intervals using pharyngeal manometry.

Justification: Traditionally, pharyngeal phase of swallowing was thought to be heavily controlled by CPG in the brainstem (Jean, 2001). Further, it has been postulated that there is reduced involvement of M1 in the pharyngeal phase of swallowing, particularly if it is decoupled from the oral phase (Huckabee et al., 2003). In addition, it has been suggested that M1 might be activated primarily in the initiation of swallowing related motor tasks associated with oral phase (Doeltgen et al., 2011; Kern et al., 2001a; Martin et al., 2004). M1 was also identified to play a role in the timing of initiation of pharyngeal swallowing (Humbert, 2010; Jefferson et al., 2009; Mistry et al., 2007; Verin et al., 2012). Since the oral phase is bypassed during this continuous reflexive task, providing an external stimulus may not elicit observable behavioural changes or changes in pharyngeal pressures generation as measured by pharyngeal manometry.

Hypotheses 5: Electrophysiological disruption of the motor cortex associated with the voluntary corticobulbar task of jaw movement in both the right and left hemispheres will result in:

- Increased irregularity of voluntary jaw movement when compared to baseline as measured by the consistency of the inter-movement intervals using EMG.
- Decreased rate of voluntary jaw movement across a 7 sec time period when compared to baseline results as measured by the number EMG peaks.

Justification: M1 has been identified to play an active role in the execution of the voluntary activation of the corticobulbar musculature (Avivi-Arber et al., 2011; Kern et al., 2001a; Martin et al., 2004). Therefore, providing an external stimulus during the execution of related tasks should disrupt the internally generated motor command if it utilizes the same neural pathway. Most of the orofacial muscles are bilaterally represented in the sensorimotor cortex (Grinevich et al., 2005; Haque et

al., 2010; Hatanaka et al., 2005; Lund & Kolta, 2006b). Therefore, disruption to either hemisphere is likely to yield observable changes in the behavioural measures or jaw movement.

Hypotheses 6 A: Electrophysiological disruption of the contralateral motor cortex associated with the voluntary corticospinal task of finger movement will result in:

- Increased irregularity of voluntary finger tapping when compared to baseline as measured by the consistency of the inter-movement intervals using finger tapping device.
- Decreased rate of finger tapping across a 7 sec time period when compared to baseline results using finger tapping device.

Hypothesis 6 B: Electrophysiological disruption of the ipsilateral motor cortex associated with the voluntary corticospinal task of finger movement will result in:

- No significant change in regularity of voluntary finger tapping when compared to baseline as measured by the consistency of the inter-movement interval using a finger tapping device.
- No significant reduction in the rate of finger tapping across a 7 sec time period when compared to baseline results using a finger tapping device.

Justification: The neural control of finger movement is well established documented and is known to require high involvement of M1 (Springer & Deutch, 1998). Finger movement is controlled by the contralateral primary motor cortex (Springer & Deutch, 1998). Thus the left primary motor cortex will be activated to control movement in the right finger and the right hemisphere for the left finger (Caroselli et al., 2006; Springer & Deutch, 1998). Therefore, providing an external stimulus during the execution of those tasks to the ipsilateral hemisphere should not disrupt the internally generated motor command as it utilizes a different neural pathway.

Significance: This study will help to clarify the role of M1 in swallowing; therefore, advancing the knowledge of swallowing neurophysiology, which is important for the development of management strategies for swallowing disorders.

Study Design: This study will investigate the influence of disrupting the neural commands from M1 to various muscles that control a number of movements of increasing complexity. These motor behaviours range from simple finger movement, to complex reflexive swallowing. This disruption will be created by stimulating the motor pathways with a single pulse TMS applied over the area of M1 representation of the target muscles.

3.1.4 Pharyngeal pressure differences between four conditions of swallowing in healthy participants. (Chapter 8)

Question: In most studies of neural control of swallowing in health and disease, swallowing has been mainly tested with discrete bolus or dry saliva swallowing conditions. This is a limitation as most people naturally complete multiple continuous swallows when ingesting liquids. Previous studies have utilized VFSS to assess the physiological differences between discrete and continuous swallowing (Chi-Fishman & Sonies, 2000; Daniels & Foundas, 2001). Recently a study by Witte et al. (2008) identified pharyngeal pressure differences between saliva and discrete water swallows using pharyngeal manometry. However, no studies have investigated the pharyngeal pressure generation differences between discrete and continuous bolus swallowing. The following question will be investigated: Are there differences in pharyngeal pressure between different conditions of swallowing, namely discrete saliva, discrete water, voluntary continuous and reflexively continuous swallowing?

Hypotheses 7: There will be significant differences in pharyngeal pressure generation between discrete saliva, discrete water, volitional continuous water, and reflexive continuous water swallowing as follows:

- Saliva swallows will produce high pharyngeal peak pressures compared to discrete and continuous water swallows.
- There will be no difference in peak amplitude between discrete and continuous water swallows.
- Discrete water and saliva swallows will produce longer pressure duration compared to continuous water swallows.
- Discrete saliva swallows will produce longer pressure duration compared to discrete water swallows.

Justification: A recent study by Witte et al. (2008) has identified differences in pharyngeal pressure generation between discrete saliva and discrete water swallows using pharyngeal manometry. Saliva swallows were produced with significantly higher pressure amplitude at the upper pharyngeal sensor only and significantly longer pressure duration at the upper and middle pharyngeal sensors compared to discrete water swallows. The authors attributed the increase of peak amplitude to more active contribution of the tongue to drive the saliva compared to water. The increased duration during saliva swallowing could be attributed to the higher viscosity, and the slower flow of saliva compared to water. Higher pressure amplitude might; therefore, be expected in saliva swallowing if compared to continuous water swallowing. Continuous flow rate in the continuous water swallowing task may result in reduced pharyngeal pressure duration as faster reaction of swallowing muscles is needed to accommodate for the constant flow compared to dry and discrete bolus swallowing (Chi-Fishman & Sonies, 2000; Daniels & Foundas, 2001).

Significance: Biomechanical differences have been identified between discrete and continuous swallowing using VFSS; however, no studies have evaluated the pharyngeal pressure generation differences between the two types of swallowing. These data will provide valuable information regarding the biomechanical differences between discrete and continuous swallowing.

Study Design: Participants will be asked to complete five blocks of trials of four different swallowing types in randomised order. Tasks included discrete saliva

swallowing, discrete 10 ml water swallow, continues volitional swallowing for 7 sec, and continuous reflexive swallowing for 7 sec. During each block of trials, continues volitional and reflexive swallowing for 7 sec, five saliva swallows and five10 ml water swallows will be completed. The behavioural difference in pharyngeal pressure generation between the swallowing types will be identified through the differences in the manometric waveform measures.

Part III: Methodology

Chapter 4: **Methodology**

This chapter introduces the methodological design that was used throughout the individual studies in this research programme. Description of methods that are specific to each study, for example description of experimental procedures and statistical analyses, will be provided in each of the individual studies.

4.1. **Power analysis:**

Power analysis was completed prior to commencement of data collection. In this research programme, significant reductions in finger tapping, eyebrow movement, and jaw movement rates were expected as a result of the effect of experimental manipulation on these measures. Due to performance variability and expected reduction of 25%, the effect sizes for those measures were in the range of 4.3 to 6.6. Power analysis showed that with such large effect sizes only 3-5 participants were required to determine if an effect was present in these measures with power equal to 0.8 (α= 0.05). Volitional swallowing number and volume per swallow were expected to be reduced as well with experimental manipulation. Due to performance variability and expected reduction of 20%, the effect sizes for those measures were in the range of 2.1 to 3.4 requiring 5 to 10 participants to demonstrate a large effect size in these measures with a statistical power of 0.8. Minimal effect of the experimental manipulation was expected on the rate and volume of swallow of the reflexive swallowing task. An expected reduction of 15% was taken for this measure resulting in an effect size of 1.4. Calculations indicated 22 to 27 participants were required to show if effect size this large was present in these measures with power equals to 0.8.

4.2. **Participants**

Based on *a priori* power analyses, 24 healthy right-handed volunteers (12 males, average age= 24.4, SD= 6.3) were recruited in this research programme. Handedness was confirmed using a modified version of the Edinburgh Handedness Inventory (Oldfield, 1971) (Appendix I). Participants expressing interest in taking part in the project were provided with an information sheet (Appendices II and III) and verbal explanation about the scope of the project and consequently provided written consent (Appendix V). All participants met the inclusion criteria of no medical history or current symptoms of dysphagia, no neurological impairments and no drug use that could potentially affect their neurological function. The inclusion criteria were confirmed using medical history questionnaire (Appendix IV) and if participants were involved in the study using TMS, they completed Transcranial Magnetic Stimulation Safety Screen (TASS) (Keel, Smith, & Wassermann, 2001) (Appendix VI). Data collection was undertaken at the Swallowing Rehabilitation Research Laboratory at the New Zealand Brain Research Institute, Christchurch. New Zealand. This research programme received ethical approval from the Upper South A Regional Ethics Committee, New Zealand.

4.3. Instrumentation

4.3.1 Finger tapping device:

A custom designed finger-tapping device[4] was developed for this research (Figure 4-1). The device consisted of two 9 Voltage Direct Current (VDC) batteries which generated an electical circuit that was activated when the finger tapper button was pressed. The 9VDC was then reduced using a voltage divider so that the output voltage will be a maximum of 5VDC (Figure 4-2). The output is then fed through individual Bayonet Neill Concelman (BNC) connectors. This device was connected to an auxiliary analogue input channel of an integrated computer system Kay Elemetrics Swallowing Workstation (KayPENTAX Inc., Lincoln Park, NJ, USA). Each finger tap completed a binary electrical circuit, which was recorded and

[4] *Designed by Michael Sheedy, Department of Medical Physics and Bioengineering at Christchurch Public Hospital, Christchurch, New Zealand.*

represented on the workstation (Figure 4-3). Digitized 12-bit samples were obtained with a sampling frequency of 500 Hz. The system software generates binary electrical waveforms as a function of time.

Figure 4-1: Custom build finger tapping device.

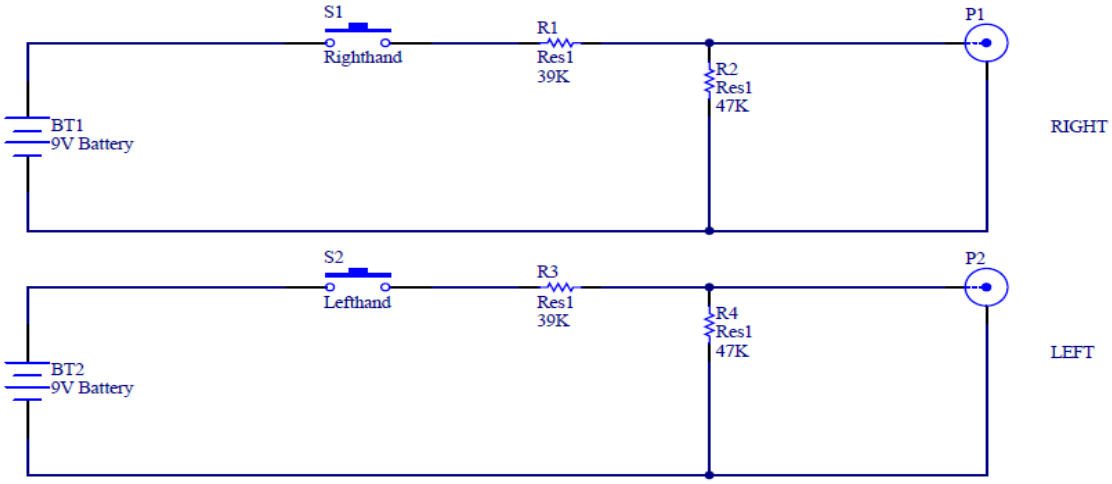

Figure 4-2: Systematic diagram of the finger tapping device.

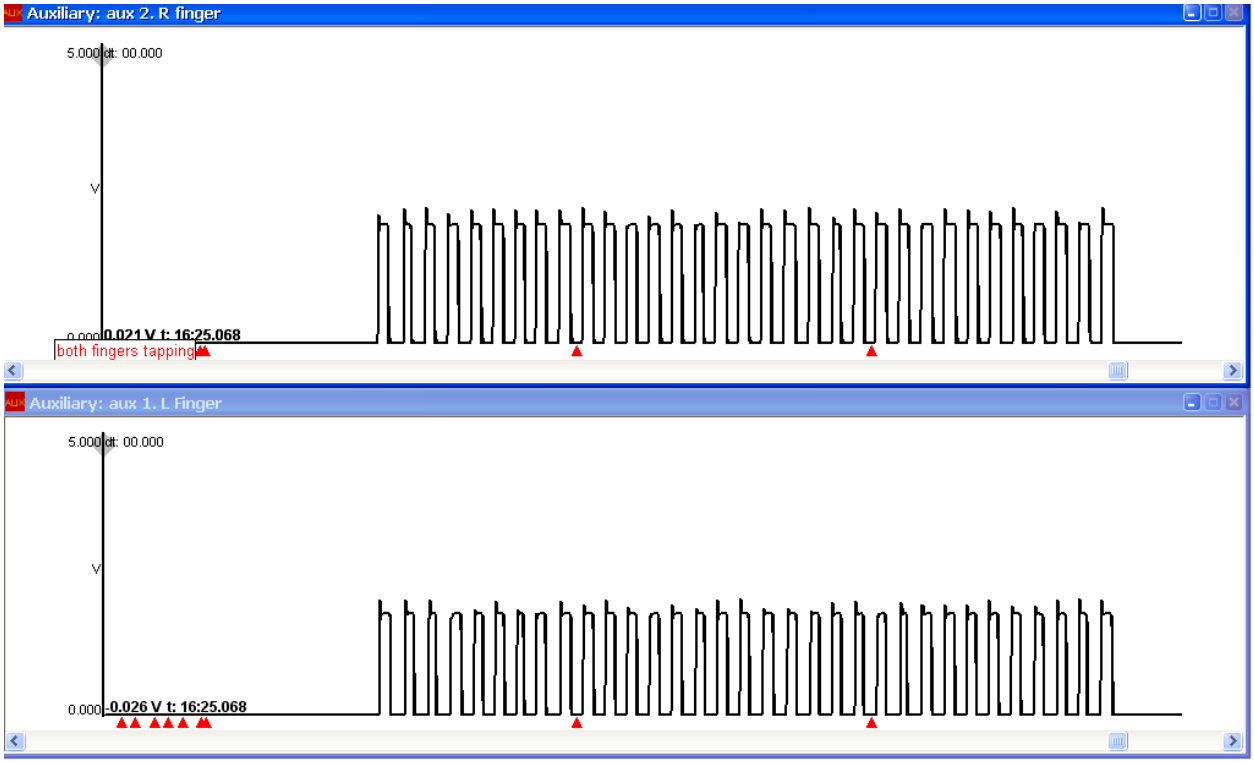

Figure 4-3: Binary peaks presented as a time by voltage waveform in the swallowing workstation for both right index finger (top) and left index finger (bottom).

4.3.2 **Surface EMG instrumentation:**

Skin cleansing swabs (70% v/v isopropyl alcohol mediswab, 36001000, BSN Medical, VIC, Australia) were used to prepare the skin surface for the recording electrodes. Surface EMG electrodes (Bipolar silver/silver chloride EMG electrodes, Norotrode 20^{TM}) were adhered to the skin surface above the eyebrows to record EMG activity during the eyebrow movement task. In addition, a single circular patch containing three silver/silver chloride electrodes (EMG, Triode^{TM} Electrode. Thought Technology Ltd) was adhered to the skin surface above the cheeks and overlying the left masseter muscle to record EMG activity during the jaw movement task. The EMG electrodes for each muscle group were connected to individual EMG channels of an integrated computer system, Kay PENTAX Digital Swallowing Workstation, (KayPENTAX Inc., Lincoln Park, NJ, USA). Digitized 12-bit samples were obtained

with a sampling frequency of 500 Hz. The raw signal was band-pass filtered (50-250 Hz) and rectified. The system software generated a time by amplitude waveform (Figure 4-4) and (Figure 4-5).

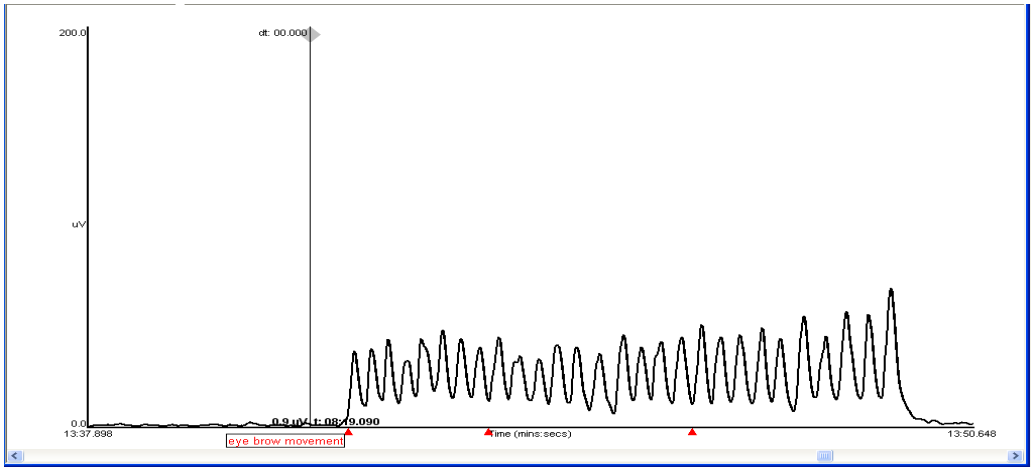

Figure 4-4: EMG peaks presented in the swallowing workstation during eyebrow movement tasks.

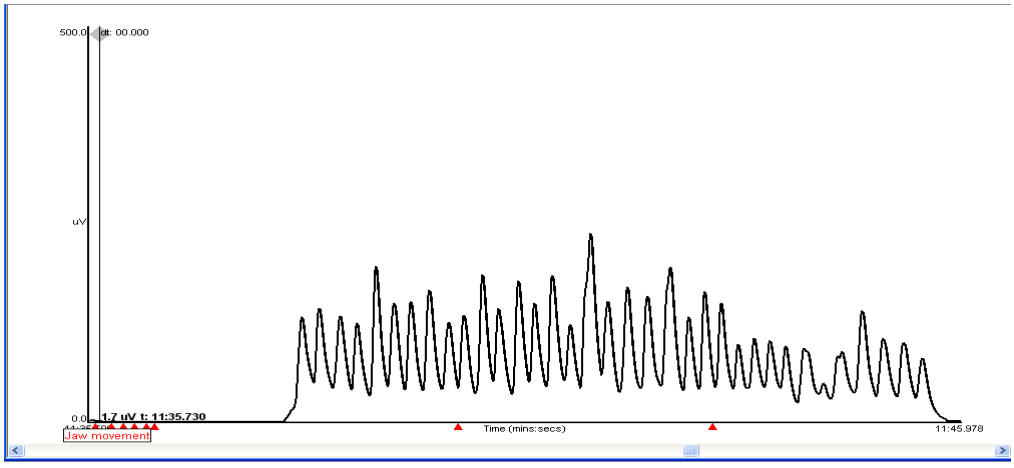

Figure 4-5: EMG peaks presented in the swallowing workstation during jaw movement tasks.

4.3.3 **Reflexive swallowing instrumentation:**

Reflexive swallowing was initiated through direct injection of water into the pharynx. A digital injection system (Angomat ® Illumena TM, 904006-K) was used to continuously inject water into the pharynx through a tube (Figure 4-6). The tube (12.5 cm long, Mixing cannula, Unomedical, Ref. 500.11.012) was inserted orally between the top and bottom left incisors to avoid contact with the uvula, thus minimizing the possibilities of eliciting a gag reflex. The tube was run through a dental bite-block that was developed for each participant to ensure standardized and safe placement of the tube in the mouth and to control for potential variation in tube placement. In order to create the bite-block, two-component Vinyl Polysiloxane Impression Material Putty (3M ESPE Express^{TM} STD) was used. While wearing medical gloves (powder-free micro-textured latex gloves, Healthcare Distributors Ltd, Christchurch, New Zealand), these materials were mixed by hand for approximately 45 sec until the formation of a cohesive mixture. The mixture was then mounted around an approximate 5cm piece of tongue depressor with minimal delay to minimize the possible hardening of the mixture. The bite-block was then placed laterally at the distal part of the oral cavity above the tongue and accurate position of the bite-block was assured by asking the participants to nod if the bite-block was placed over the posterior molar teeth. Participants were asked to bite gently on the mixture with their molar teeth until feeling the hard surface of the tongue depressor. The participants held the bite-block in their mouths for about 3 min until the mixture hardened. While the participant was holding the bite-block the researcher inserted the tube gently between the left incisor teeth and through the bite-block. The researcher then removed the bite-block from the participant's mouth and rinsed the bite-block in cold water.

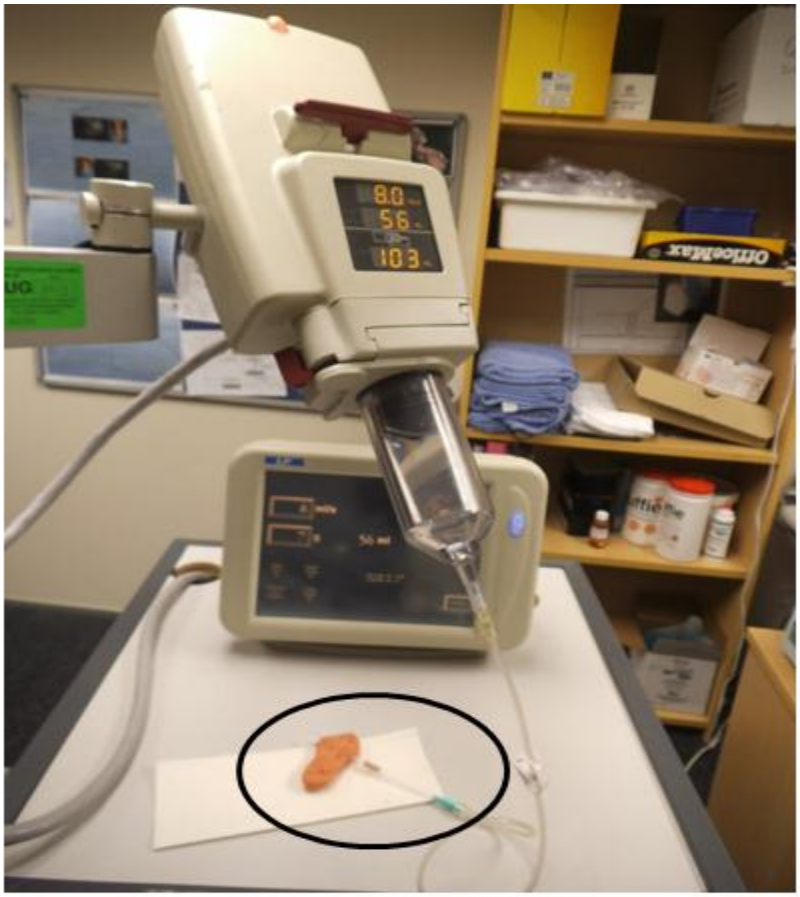

Figure 4-6: Digital injection system that was used to inject water during reflexive swallowing task. The circled item is the tube through customised dental bite-block to facilitate water injection in the pharynx during reflexive swallowing.

4.3.4 **Pharyngeal manometry instrumentation:**

A manometric catheter housing three pressure sensors (Gaeltec Pressure Transducer Model CTO/2E-3, 2.1 mm in diameter) was used to record pharyngeal pressure dynamics. The manometric catheter housed solid-state, unidirectional, posteriorly-oriented sensors spaced 20 mm between sensors one and two and 30 mm between sensors two and three (Figure 4-7). Catheter calibration was conducted according to the manufacturer's specifications prior to data collection for each participant. The catheter was calibrated at 500 mmHg at room temperature. Digitized

12-bit samples were obtained with a sampling frequency of 500 Hz. The system software generated pressure waveforms as a function of time.

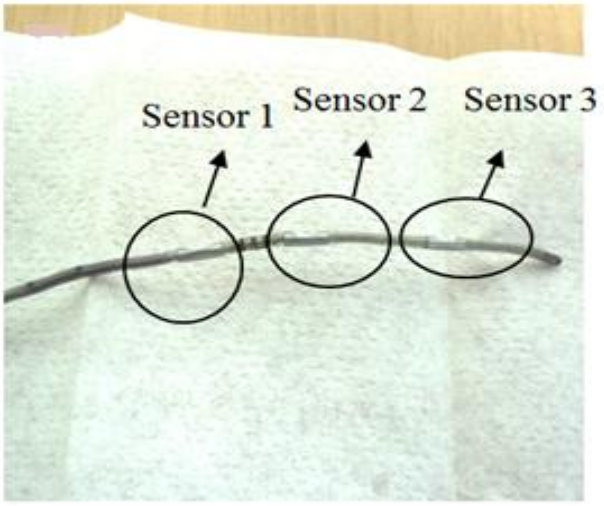

Figure 4-7: The three pharyngeal sensors outlined as follows sensor 1= upper pharyngeal sensor, sensor 2= middle pharyngeal sensor, sensor 3= UES sensor.

4.3.5 **TMS disruption instrumentation**

Skin cleansing swabs (70% v/v isopropyl alcohol mediswab, 36001000, BSN Medical, VIC, Australia) were used to prepare skin for recording electrodes. To record sEMG activity, surface electrodes (BRS-50K, Blue Sensor^{TM}, Ambu, Denmark) were connected via a shielded cable (Shielded Bio Amp cable, MLA2540, ADI Instruments) to an EMG amplifier (Dual Bio Amp, ML 135, ADI Instruments) and recording system (Powerlab 8/30, ML 870, ADI Instruments). The Scope software, which is commercially available for use with the Powerlab system, was used to record and display the EMG signals. Data were acquired at a rate of 10 kHz using a high pass filter of 10Hz. A sweep of 200ms, 50ms pre-trigger and 150ms post-trigger was recorded during discharge of the magnetic stimulator.

For swallowing tasks, a piezoelectric transducer (MP 100 Pulse Transducer, AD Instruments) was attached to the larynx to record the biomechanical activity of

the larynx during swallowing. The transducer consisted of a piezoelectric element which converted mechanical force applied to the transducer surface to an electrical signal (Figure 4-8). The transducer was connected directly to a custom built-trigger box via a BNC connector to automatically trigger the magnetic stimulator during swallowing tasks.

Figure 4-8: The pulse transducer consists of piezoelectric element which was attached to a strap to position the transducer during the swallowing tasks.

A custom-built triggering device[5] monitored the surface EMG signals, which were sent from the amplifier (Dual Bio Amp, ML 135, ADI Instruments) to the recording system (Powerlab 8/30, ML 870, ADI Instruments), and the biomechanical signals from the piezoelectric transducer (Figure 4-9). When the monitored signals breached a pre-set threshold, the trigger device produced single transistor-transistor logic impulse to discharge the TMS device. Following each discharge, the trigger device automatically blocked further impulses for two seconds.

[5] *Swallowing Stimulator, R. Dove, Department of Medical Physics and Bioengineering, Canterbury District Health Board, Christchurch, New Zealand, 2007.*

Figure 4-9: Two EMG amplifiers with shielded cable connected to the top unit (top two units), the triggering device (the middle unit) and PowerLab (the bottom unit).

Focal transcranial stimulation of the primary motor cortex was achieved using a magnetic stimulator (Magstim 200, Magstim Company Limited, Whitland, Wales) with a maximum output of 2.2 Tesla and presented with a figure-of-8 coil having an outer diameter of 90 mm (Figure 4-10).

Figure 4-10: The magnetic stimulator and the figure-of-8- coil on the top.

4.4. Procedure:

4.4.1 sEMG procedure:

Eyebrow movement task:

Participants were seated in a comfortable chair and the skin overlying the zygomatic arch and frontalis muscle on both sides of the face was cleaned with an alcohol swab before the surface EMG electrodes were adhered. Two surface EMG electrodes with inter-electrode spacing of 22 ± 1 mm were adhered to each side of to the skin surface above the eyebrows overlying the frontalis muscle to record EMG activity during the eyebrow movement task. Reference electrodes were attached over the zygomatic bone bilaterally. Placement of the electrodes was standardised by placing the active electrodes 2 cm lateral to the nasion (Figure 4-11).

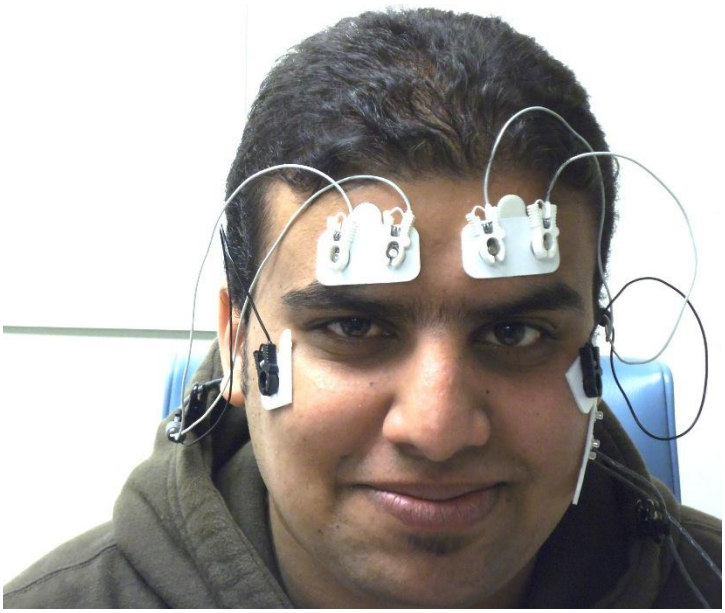

Figure 4-11: Electrodes placement for eyebrow movement task.

Jaw movement task:

The skin overlying the masseter muscle on the left side was cleaned with an alcohol swab before surface electrodes were adhered. A single patch containing three electrodes was adhered to the skin surface overlying the masseter muscle. The masseter muscle was identified by palpation when the participants were instructed to clench their teeth. Placement of the electrodes was standardized by aligning the two active electrodes parallel to the masseter muscle with the reference electrode anterior to the active electrodes. The two active electrodes were spaced evenly between the zygomatic bone and the posterior aspect of the mandibular bone (mandibular angle) (Figure 4-12).

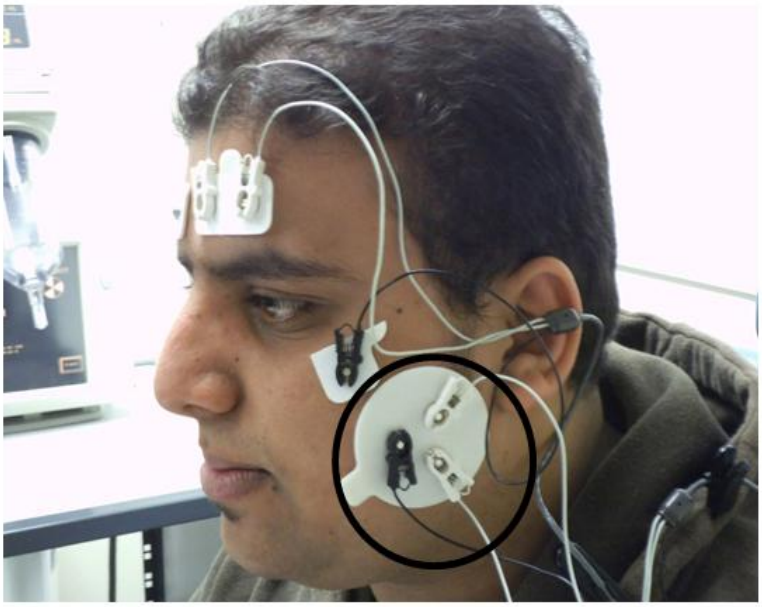

Figure 4-12: Electrodes placement for the jaw movement task.

4.4.2 Procedure for setting reflexive swallowing parameters:

After washing saliva from the bite-block, the researcher connected the tube to the infusion pump. The researcher placed the bite-block into the participant's mouth and informed them that water will be infused automatically through the tube. The researcher gently pushed the tube into the back of the oral cavity. Correct placement

of the tube was ensured when participants indicated that water was bypassing the mouth into the pharynx to elicit reflexive swallowing. Participants were then asked to bite on the tube with their incisor teeth to mark the correct placement of the tube. The rate and volume during reflexive swallowing was controlled and monitored using the injection system. To determine the appropriate rate of water flow, increments of 1 ml/s were presented until the participant indicated the maximum amount they could manage. After determining the rate and volume of water the researcher removed the bite-block and the tooth mark on the tube was marked with medical tape (3M Micropore™ hypoallergic surgical tape) to ensure standardized placement throughout the session.

4.4.3 **Manometry procedure:**

The catheter was lubricated using a lubricant gel (Lube Gel, Unitrade International (NZ) Ltd, Auckland) and inserted transnasally until it reached the upper pharynx as indicated by resistance at the posterior pharyngeal wall. When this resistance was identified, the participants were asked to look to the ceiling, thereby reducing the nasopharyngeal angle, and the catheter was passed into the pharynx. After returning their head to a normal position, participants rapidly drank water through a straw until the catheter was swallowed to approximately 40 cm from the tip of the nose into the esophagus. A pull-through technique was utilized to ensure standardized placement of the catheter in the pharynx. Gentle pull-through was applied until high pressure in upper pharyngeal sensor (top sensor) was observed indicating placement of the sensor in high pressure zone of the tonically contracted cricopharyngeus muscle (Castell & Castell, 1993). Pull-through was continued gently with the participants intermittently performing dry swallows to enable visual observation of the manometry waveforms during swallowing. Pull-through was continued until the appearance of a prototypical “M” wave on the UES sensor (lowest sensor) during swallowing which indicated placement of this sensor on the superior border of the tonically contracted UES (Castell & Castell, 1993). A number of studies have utilized M-wave method to ensure correct catheter placement (Gumbley et al.,

2008; Huckabee et al., 2005; Huckabee & Steele, 2006; Witte et al., 2008). The orientation of the manometric sensors towards the posterior pharyngeal wall was confirmed by continuous monitoring of the unidirectional markers on the catheter. Upon confirmation of correct placement, the catheter was secured to the tip of the nose with medical tape (Figure 4-13). Pharyngeal pressure was measured in the upper pharynx, middle pharynx and UES by sensors one, two, and three, respectively.

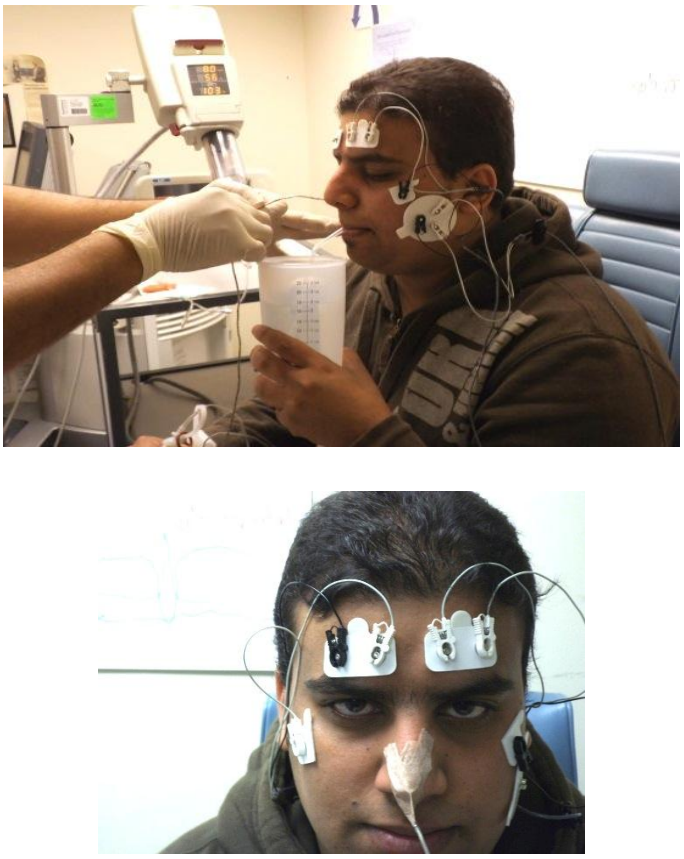

Figure 4-13: Placement of the pharyngeal manometry catheter transnasally.

4.4.4 TMS disruption procedure:

4.4.4.1 *Procedure for recording parameters for TMS measures:*

The skin over the zygomatic arch and under the chin was cleaned with an alcohol swab before three surface electrodes were adhered. To record sEMG activity during swallowing and jaw movement tasks, two surface EMG electrodes were placed at

midline over the submental musculature with an inter-electrode distance of approximately 1 cm. A reference electrode was attached to the skin surface overlaying the zygomatic bone (Figure 4-14).

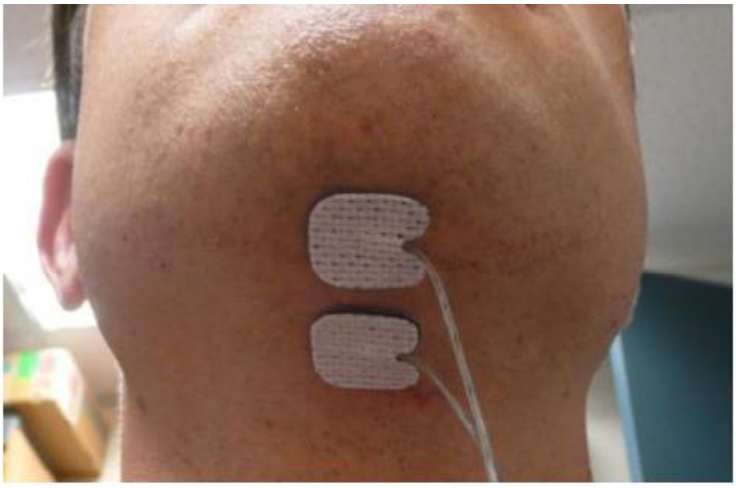

Figure 4-14: Placement of surface electrodes overlying the submental muscle group.

For the finger tapping tasks, two surface electrodes were attached over the extensor digitorum muscle (EDM) of each hand with an inter-electrode distance of 2 cm. A reference electrode was attached over the *metacarpophalangeal joint* of the fifth digit. EDM was identified by palpation of the muscle during index finger movement. Upon identification of the muscle, the placement of the electrodes over the EDM was standardized by measuring 5 cm from the medial edge of the wrist joint to the place of the first electrode (Figure 4-15).

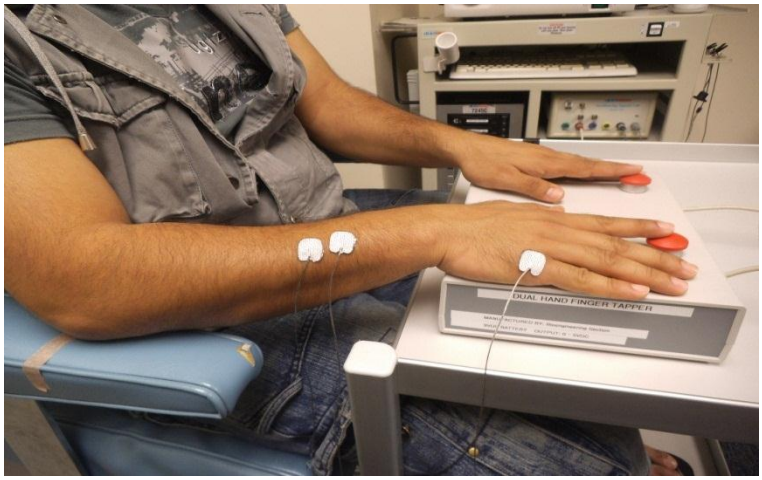

Figure 4-15: Placement of surface electrodes overlaying the EDM muscle.

4.4.4.2 ***TMS triggering procedure:***

TMS was triggered upon breach of a pre-set threshold, which was based on the EMG recording of EDM and floor of mouth muscle activation. The trigger threshold for each participant was determined prior to data collection by calculating 50% of the individual's mean sEMG peak amplitude recorded from the EDM during 10 up and down index finger movements. Similarly, the trigger threshold was set to 50% of the individual's mean sEMG peak amplitude recorded from the submental musculature group during 10 up and down jaw movement repetition. For swallowing tasks, the trigger threshold that was set to 50% of the individuals' mean electrical signal amplitude recorded by the piezoelectric transducer attached into the superior palpable edge of the thyroid cartilage during 10 dry saliva swallows (Figure 4-16). Triggering the TMS in response to pre-set threshold of electrical signal from the larynx during the swallowing tasks minimized the potential for false triggering due to oral movements not associated with pharyngeal swallowing.

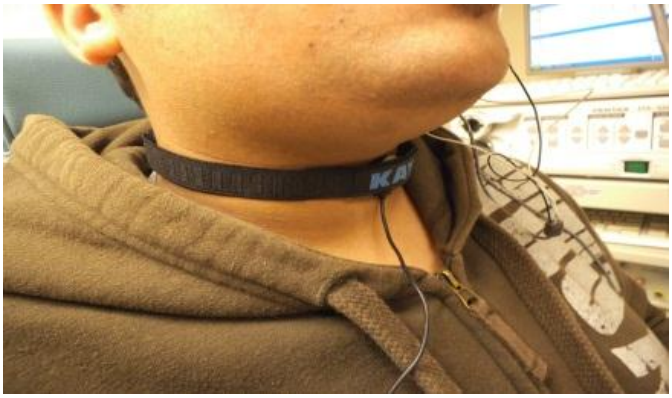

Figure 4-16: The pizeoelectric tranducer and its placement over the thyroid artilage to trigger TMS.

4.4.4.3 ***Recording MEP procedure:***

Using the protocol described by Doeltgen and colleagues (2009), the optimal site on the scalp for acquiring MEPs (hot spot) was identified for each of the target muscles. For this, the cranial vertex (Cz) was identified and marked on the scalp according to the International 10-20 Electrode System (Klem, Lüders, Jasper, & Elger, 1999). For each task, participants were asked to voluntarily contract the target muscles. While the participants activating the target muscles, starting with one of the hemispheres, TMS was applied systematically over an area approximately 4 cm anterior and 8-10 cm lateral to Cz at 60% of maximum stimulator output until MEP was recorded. This was defined as the optimal site for acquiring MEPs in that hemisphere and marked on the scalp using a water soluble pen.

The TMS threshold for evoking MEPs was then identified. For this, TMS intensity was reduced to sub-threshold intensity (no MEPs evoked in 5 successive trials) and increased in 10% increments until 5 out of 10 trials produced MEPs greater than 20μV. This intensity was identified as TMS motor threshold. Following this, stimulus response curves were recorded by increasing TMS intensity in 10% increments until MEP amplitudes plateau or max stimulator output is reached. Given that TMS disruption is intensity dependent as greater disruption was observed with higher intensities (Day et al., 1989), TMS intensity was set to a level that evoked the

largest MEP amplitudes. The same procedures were repeated in counterbalanced order over the other hemisphere as both hemispheres were investigated in this study. For swallowing tasks, the hemisphere producing the larger MEP was termed "swallowing dominant hemisphere".

4.5. **Experimental tasks**

After preparations were completed, the participants were given five min to relax and adjust to the feeling of the manometric catheter and electrodes. Participants were then given one untimed trial and one timed trial of each task with visual feedback from the computer screen. The participants were then instructed to execute the experimental tasks in randomized order without visual feedback to guide their performance. Data were stored on the swallowing workstation (Kay Elemetrics Digital Swallowing Workstation) for offline analysis.

A number of motor tasks that varied in complexity were investigated in this research programme. A subset of these motor tasks was used in each individual study of this project. These motor tasks included (i) finger tapping on a single switch with the right, (ii) left, and (iii) "bilateral index fingers", (iv) rapid up and down eyebrow movement, (v) rapid up and down jaw movements, (vi) rapid volitional swallowing through a straw, and (vii) rapid reflexive swallowing by directly injecting the water to the pharynx. Each of these tasks was performed continuously for 7 sec, as results from a small pilot study indicated that 7 sec was the optimal time to produce an adequate number of consecutive swallows without bloating during swallowing tasks. In addition to the listed continuous tasks, normal discrete saliva swallowing and discrete 10 ml water swallowing tasks were also investigated.

Participants were seated in comfortable dental chair with arm rests and were instructed on how to perform the experimental tasks as follows.

Finger tapping task:

Participants were instructed to use their index finger when performing the task and to keep their hand still on a rest space included on the tapping device, with their arms on the chair's arm rests. To complete a tap cycle, participants pushed the switch down with their index finger and then lifted the finger completely from the switch. To ensure consistency of hand placement, adhesive tape was placed at the position of the elbow in the chair arm rest after participants reported a comfortable positioning for tapping (Figure 4-17). Verbal instructions were standardized across the finger tapping tasks as follows "when I say "go", push the switch using your index finger as quickly and as consistently as you can until I say stop. Remember to lift your finger from the switch after each push".

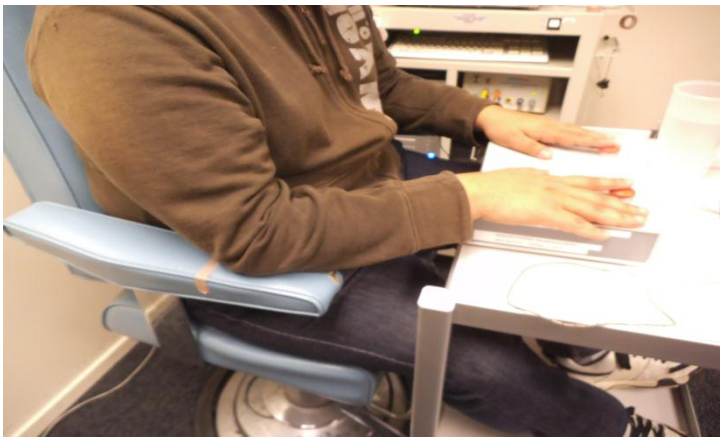

Figure 4-17: Set up for finger tapping task. Hand position in the arm rest was standardised by adhesive tape on the armrest.

Eyebrow movement task:

Participants moved their eyebrows in an up and down direction rapidly. The instructions were as follows "when I say "go", move your eyebrows up and down as quickly and as consistent as you can until I say stop".

Jaw movement task:

Participants moved their jaw in up and down direction rapidly. The instructions were as follows “when I say “go move your jaw up and down as fast and as consistent as you can until I say stop”.

Swallowing tasks:

Discrete saliva swallowing:

Participants performed five non-effortful saliva swallows at the rate of one swallow approximately every 30 seconds. The instructions were as follows “gather your saliva and when I say “go”, swallow your saliva as you normally do”.

Discrete water swallowing:

Participants swallowed 10 ml of water from a cup using a straw. The participants performed five swallows at a rate of approximately one swallow every 30 seconds. The instructions were as follows “when I say “go”, use the straw to drink the water in one swallow”.

Volitional continuous swallowing:

Participants performed continuous drinking from a cup contains 190 ml of room temperature water through a straw. The instructions were “when I say “go”, drink the water using the straw quickly until I say stop.”

Reflexive continuous swallowing:

Participants performed continuous swallowing in response to water injection directly to the pharynx. The instructions were “water will be injected directly into your throat for seven seconds, swallow when you feel that you have to swallow”.

4.6. Data processing and analysis:

Data from the above tasks were stored as time by amplitude waveforms in the swallowing workstation. Waveforms were analysed offline. Analyses were done in a 5 sec window and in 100-250μV or mmHg amplitude to increase resolution during the analyses. Rate and regularity measures were derived from the waveforms to assess the effect of the experimental manipulation in the performance of the experimental tasks.

Rate was measured by counting the number of peaks produced in 7 sec. Regularity was expressed as a co-efficient of variation (CV) using the following formula $\left[\frac{SD}{M}\right] X\ 100$, where SD is the standard deviation and M is the mean.

4.6.1 Rate measurements:

In order to assess the level of performance of the experimental tasks, the rate of tasks was measured by counting the number of task repetitions in 7 sec as follows. For *finger tapping*, the completed tap cycles from the tapping device as recorded by the swallowing workstation were calculated. The rate of *eyebrow movement and jaw movement* was measured by calculating the number of EMG peaks produced by participants during the performance of each of these tasks. For continuous *volitional* and *reflexive swallowing*, the manometric peaks recorded during performance of these tasks were calculated (Figure 4-18). In addition to the rate of swallowing, the volume of water per swallow was calculated using the following formula $\frac{\boldsymbol{A-B}}{\boldsymbol{N}}$, where A is total volume of water given to the participant, B is the volume of water left in the cup after swallowing, and N is the number of swallows completed in 7 sec.

4.6.2 **Regularity measures:**

Regularity measures were also derived from the waveforms produced by participants during the performance of the experimental tasks as follows. The regularity of *finger tapping* was assessed by manually measuring the intervals between the offset of one binary electrical circuit peak and the onset of the subsequent peak. The onset of the electrical circuit peak was defined as the time point at which the circuit leaves the baseline in rapid sharp increase towards the peak. The offset was defined as the time point at which the circuit returns to baseline after the peak.

The regularity of the *eyebrow and jaw movement* was identified by measuring the latency between the EMG peaks produced by the performance of each of these tasks. The peak of the EMG signal was defined as the highest point of the waveform. The maximum amplitude was measured in µV and was calculated automatically by the swallowing workstation by manually selecting the waveform of interest and then using the "waveform statistic" option. The maximum peak value was then displayed (Figure 4-18).

The regularity of *swallowing* was assessed by measuring the latency between manometric waveform peaks for the upper and middle pharyngeal sensors, and the latency between nadir pressure points for the UES sensor (Figure 4-19). The pharyngeal sensor peaks were defined as the highest pressure reading of these two sensors during swallowing. In contrast the UES nadir pressure was defined as the lowest pressure recording in this sensor. These measures were calculated automatically by the swallowing workstation as described in section (4.6.3. manometry data).

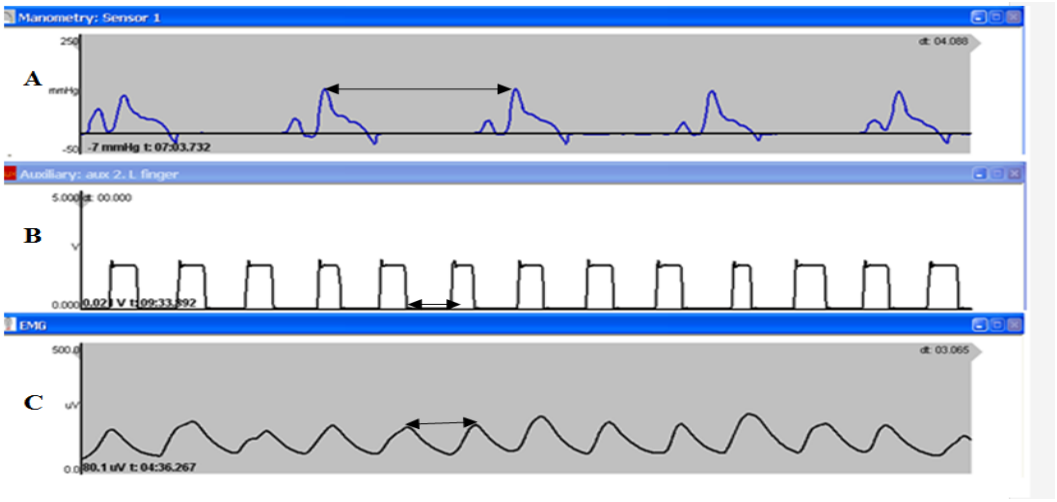

Figure 4-18: Measures of rate by counting the number of peaks produced in 7 seconds, and measures of regularity by measuring the inter-interval distance between manometric peaks for swallowing (A), inter-interval distance between binary peaks for finger tapping tasks (B), and inter-interval distancebetween EMG peaks for jaw movement and eyebrow movement tasks (C).

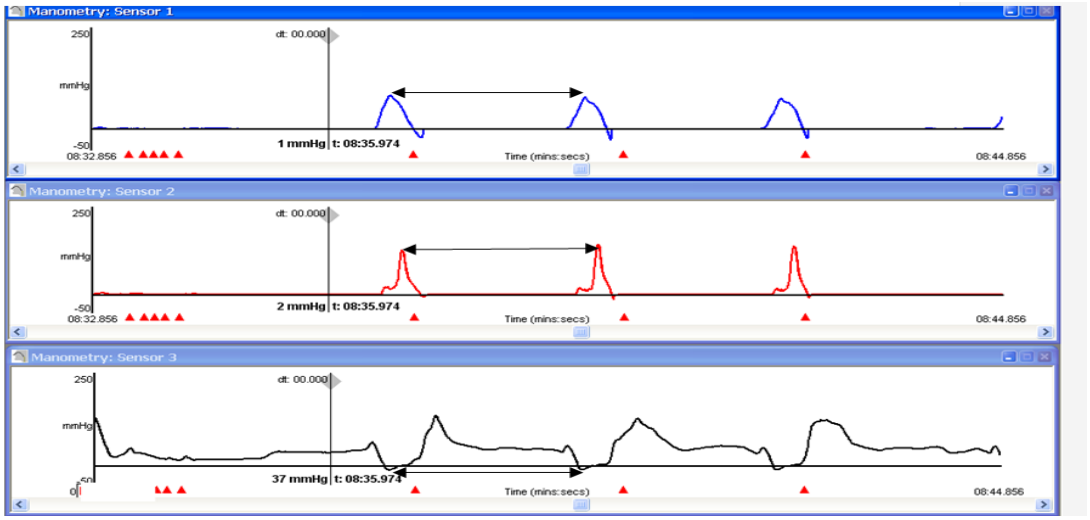

Figure 4-19: Measures of the regularity of swallowing by measuring the inter-peaks intervals of Sensors 1 and 2 (top and middle panels), and the inter-nadir pressure intervals for sensor 3 (bottom panel).

4.6.3 **Manometry data:**

The manometric waveforms were analysed offline (Figure 4-20). To allow increased resolution of the waveform, the analyses were done in 5 sec displays with an amplitude range of 100- 250 mmHg.

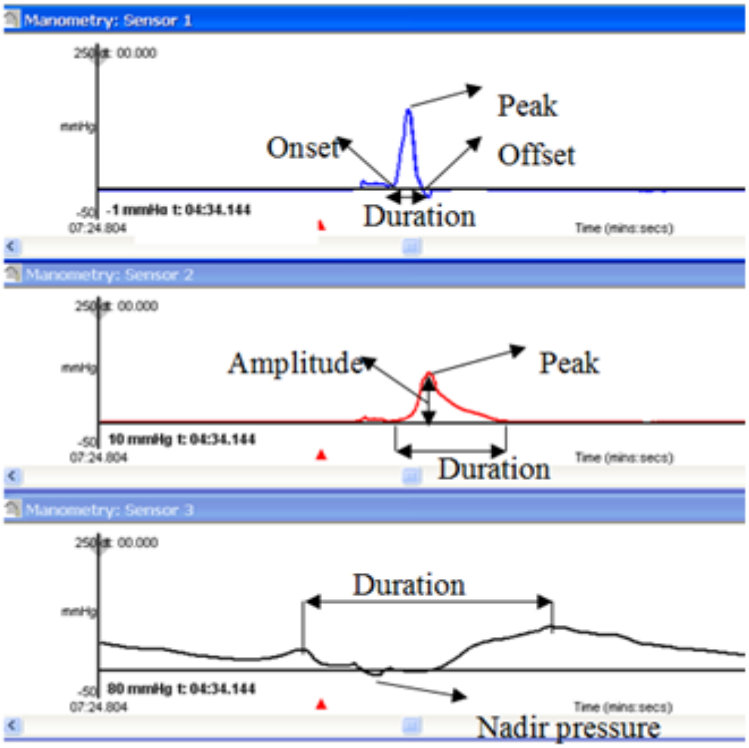

Figure 4-20: Pharyngeal manometric waveforms of a single swallow and the derived measures. Top panel displays the uppermost sensor waveform located at the upper pharynx; middle panel displays the middle sensor located at mid-pharynx; bottom panel displays the lower sensor located at the upper border of the UES.

Amplitude measurements:

Pharyngeal pressure was defined as the highest or nadir point of each waveform and was measured in mmHg. Pharyngeal pressure was calculated automatically by the swallowing workstation by manually selecting the waveform of

interest and then using the "waveform statistic" option. The maximum and minimum values of the selected waveform were displayed.

The following pharyngeal pressure measures were extracted from each waveform and tabulated for statistical analysis: (See Figure 4-20)

1- Upper and middle pharyngeal sensors peaks: the highest pressure reading of these two sensors during swallowing.
2- UES sensor (nadir pressure): the lowest pressure recording in this sensor.

Duration measurements:

The durational measures of manometric waveforms were determined by the time between the onset and the offset time points of the pressure generation. All the durational measures were derived in milliseconds (ms). The onset and offset time points were determined manually.

For the upper and middle pharyngeal sensors, the onset was defined as the time point when the waveform departed the baseline followed by a rapid constant raise toward the peak. In the case of a small increase followed by a decrease, or small increase followed by plateau, the onset was defined as the time point at which rapid and constant increase toward the peak was observed after these events.

The offset of the upper and middle pharyngeal sensors was defined as the time when the waveform returned to baseline after a rapid decrease in pressure. In the case of inconsistent decrease in pressure and without immediately returning to the baseline, the offset was defined as the time point of the lowest pressure that followed the consistent drop in pressure, but was preceded by an extended pressure period that was up to 10 mmHg above the baseline.

For the UES sensor, the onset was defined as the highest pressure point preceding a drop in pressure toward the lowest pressure point that was usually a negative value. The offset time point was the first highest point in pressure after the pressure drop.

The following pharyngeal durational measures were extracted from each waveform and tabulated for statistical analysis. (See Figure 4-20)

1- Upper and middle pharyngeal sensors duration: the time between onset of pressure increase immediately before the peak and the offset of pressure for each sensor.
2- UES sensor duration: The time between the highest pressure readings before and after the pressure drop.
3- Total duration: the time from the first observed onset of pressure at any of the sensors to the time of last observed offset of pressure at any sensor.

Part IV: Results

Chapter 5: **The effect of trials on the performance of motor behaviours.**

5.1. **Introduction:**

Most healthy subjects have the ability to learn new skills or improve existing skills given the opportunity to practice (Lee et al., 2010). Post-training improvement in corticospinal behaviours, such as sequential finger tapping, has been reported in the trained limb with a crossover of effect reported in the untrained limb (Parlow & Dewey, 1991). However, improvement in function depends highly on the nature of the task and the learning environment, including the length of the training period and the availability of visual feedback (Imamizu & Shimojo, 1995; Teixeira & Caminha, 2003).

Research suggests that cortical excitability increases in response to practicing a novel motor task as measured by increased MEP amplitude. For example, completion of a repeated thumb extension exercise increased amplitude of MEPs recorded from the extensor pollicis brevis muscle (Bütefisch et al., 2000). Similarly, one hour of functional physical therapy increased cortical motor map representation of the abductor pollicis brevis muscle (Liepert, Uhde, Gräf, Leidner, & Weiller, 2001). Repeated novel tasks have also been reported to alter excitability of the corticobulbar musculature. The excitability of cortical projections to the pharyngeal musculature increased in response to repeated water swallowing (Fraser et al., 2003); this excitability, however, was not maintained 30 minutes post training. In addition, one hour of tongue protrusion training was found to increase tongue representation on M1 and significantly decrease the TMS-evoked threshold and increase MEP amplitude (Svensson, Romaniello, Wang, Arendt-Nielsen, & Sessle, 2006). However, it is yet to be clearly documented if the change in cortical excitability reflects improvement, worsening, or no change in function of the peripheral systems. Therefore, exploring the potential changes at the peripheral level is warranted as repetitions of tasks occur frequently in research investigating motor behaviours. In

contrast, to the study by Fraser and colleagues (2003), previous research from our laboratory revealed that repetitions of saliva swallows in the same session did not change the excitability of the projections from M1 to the submental muscles (Al-Toubi, Abu-Hijleh, Huckabee, Macrae, & Doeltgen, 2011). However, when swallowing was paired with electrical stimulation, frequency dependent changes were observed in the excitability of the corticobulbar projections from M1 to the submental muscles (Doeltgen, Dalrymple-Alford, Ridding, & Huckabee, 2010). Therefore, adding sensory stimulation, i.e. water bolus or electrical stimulation, to swallowing might exaggerate the effect on cortical excitability.

M1 has been identified to play an important role in regulating volitional swallowing related tasks with reduced involvement of M1 in regulating pharyngeal swallowing (Doeltgen et al., 2011; Huckabee et al., 2003; Kern et al., 2001a; Kern et al., 2001b; Martin et al., 2004). Repetitions of swallowing tasks might yield a change in cortical excitability and therefore affect the behavioural measurements of volitional, but not the more reflexive phase of swallowing or the pharyngeal pressure generation where less cortical involvement is needed.

Investigation of the effects of repetitions of motor tasks on performance provides important baseline data for the methodologies employed in this research programme. It is possible that repeated motor tasks in this research programme can be classified as a "novel skill", because the context and frequency of the tested conditions would not normally occur in everyday situations. Frequent repetitions of motor tasks during a session might yield increased or decreased performance, due to factors such as practice or fatigue. Therefore, it is warranted to test the effects of these factors during the analysis to strengthen the findings, reduce variability and increase power. The aim of this study was therefore to identify the effects of repeating measures on the performance of corticospinal and corticobulbar motor behaviours. Based on the above mentioned studies, the following hypotheses were tested: (The hypotheses have been elaborated in the hypotheses section of this thesis, Chapter 3).

Hypothesis 1: Performing multiple trials of the voluntary corticospinal task of index finger movement will result in significant increase in the regularity and rate of finger movement.

Hypothesis 2: Performing multiple trials of the voluntary corticobulbar tasks of jaw movement and eyebrow movement will result in significant increase in the regularity and rate of these two tasks.

Hypothesis 3: Performing multiple trials of volitional continuous swallowing will result in significant increase in rate, regularity, average volume per swallow but not pharyngeal pressure.

Hypothesis 4: Performing multiple trials of reflexive continuous swallowing will result in no significant change in rate, regularity, volume of liquid per swallow and pharyngeal pressure.

5.2. Methodology:

5.2.1 Research tasks:

Each participant was scheduled for a single session. Five blocks of trials of each of the tasks listed below were completed in randomized order to evaluate the research hypotheses. During each block of trials, participants performed the research tasks in isolation and without experimental disruption for 7 sec. The research tasks included finger tapping on a single switch with the right, left, and bilateral index fingers, up and down eyebrow movement, up and down jaw movement, volitional swallowing through a straw, and reflexive swallowing by directly injecting the water to the pharynx. All conditions were performed as rapidly and consistently as possible in randomized order. The procedure for each task and outcome measurements were described in further detail in the methodology section of this thesis (Chapter 4).

5.2.2 **Data preparation:**

Data from the above tasks were stored in the Kay Elemetrics Digital Swallowing Workstation™ computer for offline analysis. For the bimanual task of bilateral finger tapping the index finger from each hand was considered a separate dependent measure, therefore bilateral finger tapping - right finger and bilateral finger tapping - left finger were included in the analysis. Rate was measured by counting the number of peaks produced in 7 sec. Regularity however, was expressed as a CV. For swallowing tasks, the number of swallows and the volume of liquid per swallow were calculated. The regularity of swallowing tasks for each of the three manometry sensors was expressed as CV. Furthermore, for swallowing tasks, the amplitude and duration of the manometry waveforms representing the pressure generated by pharyngeal muscles during swallowing were also calculated for each swallowing event. A detailed description of the data processing for each task is provided in the methodology section of this thesis (Chapter 4).

5.2.3 **Statistical analysis:**

Repeated Measures Analyses of Variance (RM-ANOVA) was used to identify within subjects differences. Rate and regularity data for non-swallowing tasks were run in two separate one-way RM-ANOVAs with ***Trials*** as factor. Swallowing behavioural measurements, rate (number of swallows and volume per swallow) and regularity data were run in two separate two-way RM-ANOVAs with ***Swallowing type*** (volitional and reflexive) and ***Trials*** as factors. In addition, the manometric measures of pharyngeal pressure amplitude and duration were run in two separate two-way RM-ANOVAs with ***Swallowing type***, and ***Trials*** as factors.

When significant main effects were present, post-hoc analyses (pairwise comparisons) were then performed to explore the strength of main effects and the pattern of interaction between experimental factors. When the assumption of sphericity was violated, a correction to the degrees of freedom was applied using Greenhouse- Geisser. Bonferroni correction was applied to counteract the effect of

multiple comparisons during post-hoc analysis. Adjusted P values were reported when Bonferroni correction was applied. SPSS 19.0 was used with an *a priori* significance level set at P= 0.05. Data are presented as mean ± standard errors (SE) unless otherwise indicated.

5.3. **Results:**

5.3.1 **Non-swallowing motor behaviours:**

Mean rates and (SE) for non-swallowing tasks across trials are displayed in Table 5-1.

Table 5-1: Mean and (SE) of rates of non-swallowing motor behaviours across trials.

	Trial 1	**Trial 2**	**Trial 3**	**Trial 4**	**Trial 5**
R-Finger Tapping	29.625 (1.272)	29.708 (0.859)	31.000 (1.097)	30.333 (1.056)	31.083 (0.880)
L-Finger Tapping	28.583 (1.181)	30.250 (0.939)	30.583 (0.897)	30.625 (0.901)	30.708 (0.951)
Both Finger Tapping-R	27.292 (1.336)	28.833 (1.134)	29.083 (0.925)	29.625 (0.840)	28.167 (1.044)
Both Finger Tapping-L	27.458 (1.298)	28.500 (1.102)	29.000 (1.020)	30.042 (.721)	29.833 (0.926)
Eyebrow movement	20.708 (0.743)	20.667 (0.777)	20.875 (0.716)	21.000 (0.860)	21.500 (0.745)
Jaw movement	19.625 (1.182)	21.167 (1.239)	21.792 (1.113)	21.875 (1.207)	22.000 (1.173)

Note: R= Right, L= Left.

5.3.1.1 ***Finger tapping tasks:***

Rate measures: There was a significant main effect of ***Trials*** on the rate of left finger tapping ($F_{(4, 92)} = 3.47$, $p = 0.011$), and bilateral finger tapping - left finger ($F_{(2.4, 55.15} = 3.23$, $p = 0.039$). There was however no significant main effect of ***Trials*** on the rate of right finger tapping ($F_{(2.39, 54.92)} = 1.11$, $p = 0.345$) or bilateral finger tapping - right finger ($F_{(4, 92)} = 1.8$, $p = 0.136$).

Bonferroni-corrected post-hoc analysis revealed no significant differences in rate of left finger tapping between trials ($p > 0.05$). Likewise, when Bonferroni-correction was applied, post-hoc analysis revealed that during the bilateral finger tapping task the rate of left finger tapping (bilateral finger tapping - left finger) was not significantly different between trials ($p > 0.05$).

Regularity measures: There were no significant main effects of ***Trials*** on the regularity of any of the finger tapping tasks as follows: right finger tapping ($F_{(2.76, 63.46)} = 0.70$, $p = 0.543$), left finger tapping ($F_{(2.61, 60.02)} = 1.23$, $p = 0.306$), bilateral finger tapping – right finger ($F_{(4, 92)} = 1.64$, $p = 0.172$), or bilateral finger tapping - left finger ($F_{(2.96, 68.06)} = 0.86$, $p = 0.466$).

5.3.1.2 ***Jaw movement task:***

Rate: There was a significant main effect of ***Trials*** on the rate of jaw movement ($F_{(2.95, 67.95)} = 3.60$, $p = 0.010$). Bonferroni-corrected post-hoc analysis revealed no significant differences between the trials ($p > 0.05$)

Regularity measure: There was no significant main effect of ***Trials*** on the regularity of jaw movement tasks ($F_{(3.16, 72.59)} = 0.743$, $p = 0.54$).

5.3.1.3 ***Eyebrow movement task:***

Rate measures: There was no significant main effect of ***Trials*** on the rate of eyebrow movement task ($F_{(4, 92)} = 0.84$, $p = 0.506$).

Regularity measure: There was no significant main effect of ***Trials*** on the regularity of eyebrow movement tasks ($F_{(4, 92)} = 0.59$, $p = 0.674$).

5.3.2 Swallowing tasks:

Rate measures: Results revealed significant main effects of ***Swallowing type*** on number of swallows ($F_{(1, 23)} = 5.37$, $p= 0.030$) and volume per swallow ($F_{(1,23)} = 16.53$, $p< 0.001$). There were no significant effects of ***Trials*** on the number of swallows ($F_{(4, 92)} = 2.16$, $p= 0.080$) or volume per swallow ($F_{(2.7, 62.2)} = 0.57$, $p= 0.618$). Furthermore, there was no significant ***Swallowing type*** by ***Trials*** interaction for the number of swallows ($F_{(2.67, 61.28)} = 1.62$, $p= 0.198$) or volume per swallow ($F_{(2.76, 63.94)} = 2.23$, $p= 0.098$).

Bonferroni-corrected post-hoc analysis revealed that participants swallowed significantly more frequently during volitional swallowing (M= 7.28, SE= 0.31) than during reflexive swallowing (M= 6.27, SE= 0.34, $p = 0.030$). The volume per swallow during volitional swallowing (M=11.57, SE= 1.53) was significantly higher than volume per swallow during reflexive swallowing (M= 5.87, SE= 0.31, $p< 0.001$) as shown in Figure 5-1.

Regularity measure: There were no significant main effects of ***Swallowing type*** on the regularity of swallowing at the upper pharyngeal sensor ($F_{(1, 23)} = 2.97$, $p = 0.098$), middle pharyngeal sensor ($F_{(1, 23)} = 3.93$, $p = 0.059$) and UES sensor ($F_{(1, 23)} = 0.818$, $p = 0.38$) during swallowing tasks. Furthermore, there were no significant effects of ***Trials*** on the regularity swallowing at the upper pharyngeal sensor ($F_{(2.42, 55.56)} = 1.41$, $p = 0.253$), middle pharyngeal sensor ($F_{(4, 92)} = 0{,}138$ $p = 0.968$) and UES sensor ($F_{(1.85, 42.5)} = 1.01$, $p = 0.367$) during swallowing tasks. Likewise, there were no significant ***Swallowing type*** by ***Trials*** interactions for the regularity of all manometric sensors during swallowing tasks [upper pharyngeal sensor ($F_{(2.62, 60.17)} = 0.67$, $p = 0.556$), middle pharyngeal sensor ($F_{(4, 92)} = 1.07$, $p = 0.375$) and UES sensor ($F_{(1.78, 40.92)} = 1.12$, $p = 0.33$).

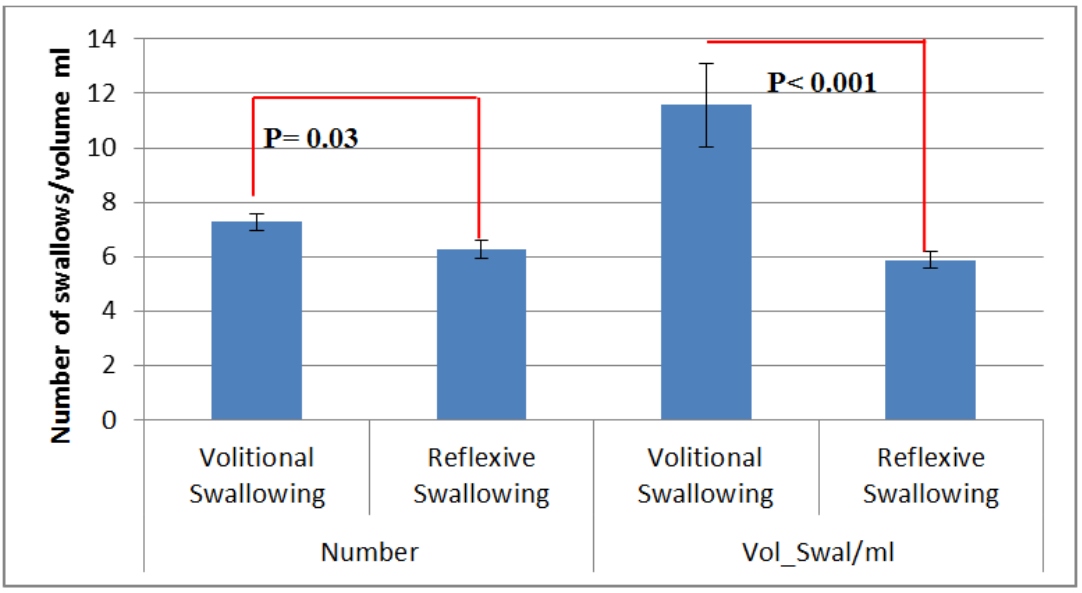

Figure 5-1: Effect of Swallowing type on rate and volume per swallow. Error Bars represents SE. Vol_Swal / ml = Volume per swallow.

5.3.3 Effects of trial on pharyngeal pressure measures during volitionally and reflexively initiated pharyngeal swallowing

5.3.3.1 *Pharyngeal pressure amplitude measurement:*

There were no significant main effects of ***Swallowing type*** on the amplitude of upper pharyngeal sensor ($F_{(1, 23)} = 0.71$, $p = 0.793$), middle pharyngeal sensor ($F_{(1, 23)} = 1.02$, $p = 0.323$) and UES sensor ($F_{(1, 23)} = 3.77$, $p = 0.064$). Further, there were no significant effects of ***Trials*** on the amplitude of upper pharyngeal sensor ($F_{(1.05, 24.1)} = 1.19$, $p = 0.289$), middle pharyngeal sensor ($F_{(4, 92)} = 1.87$, $p = 0.123$) and UES sensor ($F_{(2.59, 59.45)} = 0.83$, $p = 0.467$). In addition, there were no significant ***Swallowing type*** by ***Trials*** interactions for the amplitude of upper pharyngeal sensor ($F_{(1.05, 24.1)} = 0.75$, $p = 0.400$), middle pharyngeal sensor ($F_{(4, 92)} = 0.34$, $p = 0.850$) and UES sensor ($F_{(2.52, 57.99)} = 1.23$, $p = 0.305$).

5.3.3.2 ***. Pharyngeal pressure durational measurement:***

Swallowing type did not produce significant main effects on the duration of upper pharyngeal sensor ($F_{(1, 23)} = 0.17$, $p = 0.685$), middle pharyngeal sensor ($F_{(1, 23)} = 0.00$, $p = 0.987$) and UES sensor ($F_{(1, 23)} = 0.08$, $p = 0.775$). Similarly, there were no significant main effects of ***Trials*** on the duration of upper pharyngeal sensor ($F_{(4, 92)} = 0.29$, $p = 0.887$), middle pharyngeal sensor ($F_{(2.82, 71.27)} = 1.20$, $p = 0.315$) and UES sensor ($F_{(4, 92)} = 1.39$ $p = 0.243$). Likewise, there was no significant ***Swallowing type*** by ***Trials*** interactions for the duration of upper pharyngeal sensor ($F_{(4, 92)} = 0.52$, $p = 0.720$), middle pharyngeal sensor ($F_{(2.97, 68.31)} = 0.91$, $p = 0.441$) and UES sensor ($F_{(4, 92)} = 2.01$ $p = 0.100$).

5.4. Discussion:

This study investigated the within-session performance consistency of corticobulbar and corticospinal motor behaviours. Repetitions of tasks within-session did not influence the rate or the regularity of the voluntary corticospinal motor tasks of right, left and bilateral index finger tapping. Furthermore, task repetitions did not influence the rate and regularity of the voluntary corticobulbar tasks of eyebrow movement and jaw movement. Repeating the swallowing tasks during a session did not affect the rate and regularity of volitional and reflexive swallowing or the pharyngeal pressure as measured by pharyngeal manometry. Therefore it is safe to speculate that the effects seen in studies investigating experimental manipulation on motor behaviours are primarily the result of experimental manipulation with limited, if any, influence of task repetitions within a session.

It was proposed that repetitions of corticospinal motor tasks within a session would increase the rate and regularity of these tasks due to practice effect. This was not confirmed in the present study. Lack of effect may be attributed to the simplicity of the tapping tasks as participants were instructed to use index fingers to tap on

single switch. Tapping with a single finger on a single switch may not pose a challenge; therefore it may not represent a "novel task" with limited practice effect. Practicing an automated simple task, walking, for 30 minutes did not alter the motor cortical excitability for the lower limb tibialis anterior and soleus muscles (Thompson & Stein, 2004). However, a significant increase in cortical excitability was identified when walking was paired with electrical stimulation, which provided a "novel task" context.

Repeated thumb abduction resulted in increased cortical excitably as evident by increased MEP amplitude recorded from the extensor pollicic brevis muscle (Bütefisch et al., 2000); however, whether there was change in the peripheral performance was not reported. The increase in cortical excitability may be an adaptation mechanism for increased demand from the peripheral muscles to ensure consistency of the task performance rather than reflecting change in the peripheral performance. Cortical excitability was not measured in the current study; therefore, it hinders the direct comparison of these results. Our data revealed lack of significant effect of task repetitions on the regularity of finger tapping tasks. Previous studies suggested that measures of regularity are more sensitive than rate to detect the effect of experimental disruption during finger tapping tasks (McFarland & Ashton, 1978c). Lack of effect of task repetitions on tapping regularity suggests that repetition of tasks within a session does not alter the performance of corticospinal tasks.

Eyebrow movement is a task that is not performed frequently; therefore, one would expect a change in performance with repetitions of this task due to practice or fatigue. This was not evident in the current study. Again, one could assume that limited practice time and trials were not sufficient to yield an effect on the performance. Another possible explanation is that eyebrows could only move in one direction, up and down; therefore, it is an easier task to perform than tasks that could move in more than one direction. The decreased complexity of this task may have been the reason for lack of significant change in rate and regularity throughout the session.

Lack of significant influence of task repetition on jaw movement in the present study could be due to the fact that this type of movement is extensively used in everyday activities such as chewing. Chewing is a circular motion that requires the jaw to move up and down as well as from the side to side, and it is usually performed at a slow rate. Limiting the jaw movement to an up and down motion with high rate, as in the present study, is different from chewing. Therefore, jaw movement was performed at slower rate in the beginning of the session as indicated by the mean and SE presented in (Table 5-1). This indicates that performing tasks at a higher rate than the everyday life may alter the task performance slightly at the beginning. On this note, performing 200 discrete water swallows at a rate of a swallow every five seconds was found to alter the cortical excitability as shown by increased MEP amplitude from the pharyngeal muscles (Fraser et al., 2003). However, this increase in cortical excitability might be an adaptation of the neural system to the increased frequency of tasks performance to ensure consistency of performance in the increased demand from the peripheral system. In fact, the performance of 60 repetitions of a voluntary corticobulbar task of discrete saliva swallowing with at least 10 sec intervals between swallows did not affect the corticobulbar excitability associated with the submental muscle group (Al-Toubi et al., 2011). This might be due to that participants were given enough time to prepare for the task, thus less demand on the neural system.

The results of the present study revealed lack of significant effect of task repetition on the behavioural measures of the volitional swallowing task. Fraser et al. (2003) reported that repetition of discrete water swallowing resulted in a significant increase in MEP amplitude. Given the high frequency of task repetition in the study by Fraser et al. study, 200 swallows at a rate of one swallow every 5 sec, this task could be considered a novel task as normal human being do not usually swallow at this high rate. The lack of influence of task repetition on volitional swallowing task could be due to the high frequency of performing volitional swallowing in everyday life.

One could argue that reflexively initiated pharyngeal swallowing is a novel task given the unnatural way of the initiation. Therefore, one might expect an effect

of the repetition of this task on swallowing rate and regularity; however, this was not evident in the present study. It is well established that the pharyngeal phase of swallowing require reduced involvement from the cortex due to its more reflexive nature than oral phase (Jean, 2001; Jean & Dallaporta, 2006). Therefore, repetition of a more reflexive act in a healthy system might not be sufficient to produce significant changes in performance. This is further supported by the lack of significant effect of swallowing task repetitions on the pharyngeal pressure generation mechanisms.

5.5. **Conclusion:**

Repetition of tasks in a single session did not affect the performance of voluntary corticospinal and corticobulbar tasks. Furthermore, repetition of tasks does not seem to affect the performance of complex corticobulbar tasks, i.e. swallowing. This may be attributed to the high number of repetitions of those tasks in everyday life and to the reduced involvement of the cortical regions in controlling the more reflexive components of the pharyngeal phase of swallowing. Therefore, it is speculated the effect seen in studies investigating the effect of experimental manipulation on motor behaviours is mainly due to the experimental manipulation with minimal, if any, influence of task repetitions.

Chapter 6: **The effect of dual-task interference on pharyngeal swallowing.**

6.1. **Introduction:**

The DT paradigm is a non-invasive behavioural method that has been used for a number of years to assess functional lateralization and neural organization (Cherry & Kee, 1991; Hellige & Kee, 1990). In this paradigm participants are usually asked to perform two tasks simultaneously and an effect on one or both tasks is likely to result if the control of these tasks are closely associated in the CNS system (Pashler, 1994). The effect of the DT paradigm is explained by a number of theories with the most accepted theories are the functional cerebral space and the capacity sharing theories. The functional cerebral space theory indicates that the interference of tasks during dual task performance suggests a close neuroanatomical representation and overlapping neural control of the two tasks (Kinsbourne & Hicks, 1978). The capacity sharing theory indicates the effect of DT interference as a result of sharing mental resources, or processing capacity among tasks (Kinsbourne & Hiscock, 1983; Pashler, 1994).

The DT paradigm has been utilized to investigate lateralization of swallowing in a group of right-handed adults (Daniels et al., 2002; Daniels et al., 2006). Daniels et al. (2002) paired swallowing with rapid index finger tapping a silent word repetition task to determine hemispheric specialization in swallowing. This study reported significant reduction of finger tapping rate and average volume per swallow when paired with silent word repetition. Furthermore, significant reduction of finger tapping rate was also found during concurrent performance of swallowing tasks. These researchers further expanded the design of the earlier study by adding a right hemisphere lateralized task (visuospatial line-orientation task)(Daniels et al., 2006). The authors reported significant reduction of average volume per swallow when paired with silent word repetition. Furthermore, significant reduction of number of

swallows was found during concurrent performance of finger tapping, and concurrent performance of visuospatial line orientation. These results suggest competitions for neural resources between tasks and reduced processing capacity hence the effects observed on tasks when performed concurrently. Both studies support the view that swallowing is bilaterally represented with different roles of each hemisphere to mediate swallowing. The possibility of shared cognitive attention was not discussed in the above studies.

There are limitations to these studies that may influence interpretation. Both studies utilized tasks that were not quantifiable, silent word repetition and visuospatial line orientation, therefore the magnitude of effects between tasks cannot be tested in these studies. In order to increase confidence in verifying lateralization patterns, both tasks in the DT paradigm should be quantified. Furthermore, pairing two motor tasks that utilize different neural pathways, such as finger tapping and swallowing represent a further confound to these studies. Studies pairing two motor tasks that utilize similar neural pathways are needed to reduce degrees of freedom and interpret task interference, thus revealing clearer representation of task prioritization and competition for resources within the hemisphere, cortical region and neural pathways. This would provide an opportunity to investigate the functional contribution of specific brain areas in the execution of motor behaviour, rather than limiting the investigation to the hemispheric lateralization of the tasks. In prior DT paradigm research, volitional continuous swallowing was tested, which may have input from M1 due to the involvement of oral structures in the execution of this type of swallowing. The inclusion of reflexive swallowing tasks in studies utilizing DT paradigm will facilitate the identification of the role of the cortex, M1, in the control of swallowing. Further, inclusion of both swallowing tasks will allow highlighting the difference in neural control between volitional and reflexive swallowing by comparing the effect of the DT paradigm on both tasks.

No studies have investigated the effect of DT on reflexively initiated swallowing. Furthermore, no studies have investigated the effect of DT disruption on specific biomechanics of swallowing, such as pharyngeal pressures generation. Therefore the aim of this research was to clarify the role of M1 in pharyngeal

swallowing by pairing swallowing with motor tasks that utilize similar neural pathways, corticobulbar tasks, and investigating two types of swallowing: volitional and reflexive, that require different levels of cortical involvement.

6.2. **Hypotheses:**

M1 plays important role in the execution of voluntary corticospinal tasks (Caroselli et al., 2006; Springer & Deutch, 1998), and voluntary corticobulbar tasks (Avivi-Arber et al., 2011; Kern et al., 2001a; Martin et al., 2004; Sessle, 2009). In addition, it has also been suggested that M1 plays important role in regulating volitional swallowing with reduced involvement in regulating reflexively initiated pharyngeal swallowing (Doeltgen et al., 2011; Huckabee et al., 2003; Kern et al., 2001a; Kern et al., 2001b; Martin et al., 2004). The orchestration of pharyngeal swallowing is thought to be heavily controlled by CPG and is thought to be modulated through supramedullary regions (Jean, 1990, 2001; Miller & Chang, 1999). Therefore, pairing tasks that share neural resources from M1 might yield a change in the performance of one or both of the tasks. In contrast, pairing tasks that utilize neural resources from distinct areas in the brain, such as finger tapping and reflexive swallowing, may not result in significant effects on either task when they performed concurrently.

Based on the above mentioned studies, the following hypotheses were tested: (The hypotheses have been elaborated in the hypotheses section of this thesis, Chapter 3).

Hypothesis 1: The performance of concurrent finger tapping and volitional continuous water swallowing will result in reduction of the rate, volume per swallow and regularity of volitional swallowing, as well as reduction in rate and regularity of finger tapping. However, there will be no significant change on pharyngeal pressure measures of swallowing.

Hypothesis 2: The performance of concurrent finger tapping and reflexive continuous swallowing will neither affect rate, volume per swallow, regularity and

pharyngeal pressure measures of swallowing, nor will it affect rate and regularity of finger movement.

Hypothesis 3: The concurrent performance of eyebrow movement and volitional continuous water swallowing will result in significant reduction in rate, volume per swallow, and regularity of swallowing, as well as a reduction in rate and regularity of eyebrow movement. However, there will be no significant effect of the experimental task on pharyngeal pressure measures of swallowing.

Hypothesis 4: In contrast, the concurrent performance of eyebrow movement and reflexive continuous water swallowing will result in no significant change in rate, volume per swallow, and regularity of swallowing, as well as no change in rate and regularity of eyebrow movement. In addition, there will be no significant change on pharyngeal pressure measures of swallowing.

Hypothesis 5: The performance of concurrent finger tapping and eyebrow movement will result in significant reduction in rate and regularity of finger tapping, and eyebrow movement.

6.3. **Methodology:**

6.3.1 **Research tasks:**

Research participants attended a single session. Following experimental set up, (see methodology section of this thesis, Chapter 4), one trial of each experimental task outlined below was completed in randomized order. Research tasks were: (i) finger tapping on single switch with the right index finger (ii) finger tapping on single switch with the left index finger, (iii) bilateral index finger tapping, (iv) eyebrow movement, (v) volitional swallowing through a straw and (vi) reflexive swallowing in response to direct injection of water to the pharynx. Tasks were performed in isolation as a baseline measure. Further, these tasks were performed concurrently with another task for the DT paradigm as follows:

(1) Finger tapping with the right index finger during:

- Volitional water swallowing.
- Reflexive water swallowing.
- Eyebrow movement.

(2) Finger tapping with the left index finger during:

- Volitional water swallowing.
- Reflexive water swallowing.
- Eyebrow movement.

(3) Bilateral index finger tapping during:

- Volitional water swallowing.
- Reflexive water swallowing.
- Eyebrow movement.

(4) Eyebrow movement during:

- Volitional water swallowing.
- Reflexive water swallowing.

All tasks were performed in randomized order for 7 sec as rapidly and consistently as possible. The procedure for each task and outcome measurements were described in detail in the methodology section of this thesis (Chapter 4).

6.3.2 **Data preparation:**

Data from the above tasks were stored in the swallowing workstation for offline analysis. For the bimanual task of bilateral finger tapping the index finger from each hand was considered a separate dependent measure; therefore, “bilateral

finger tapping - right finger" and "bilateral finger tapping - left finger" were included in the analysis. The following measures were derived from the data:

Rate:

Rate was measured by counting the number of peaks produced in 7 sec. In addition to the rate, the volume of liquid per swallow was also calculated for swallowing tasks.

Regularity:

Regularity was expressed as a CV of the intervals between binary peaks produced by the finger tapping device during finger tapping tasks, or the interval between peaks of EMG amplitude during eyebrow movement. The regularity of swallowing tasks was expressed as CV of the intervals between the manometric peaks produced by each of the three manometric sensors. Each sensor was considered a dependent variable, so the CVs from each sensor were included in the analysis.

Manometric measures for the swallowing tasks:

The amplitude and duration of the manometric peaks representing the pressure generated by pharyngeal muscles were also calculated from the swallows performed in isolation and compared to the swallows performed in DT.

Detailed description of the data processing for each task is provided in the methodology section of this thesis (Chapter 4).

6.3.3 **Statistical analysis:**

RM-ANOVA was used to identify within-subject differences. Rate and regularity data for non-swallowing tasks were run in two separate one-way RM-ANOVAs with ***Task*** as a factor as follows:

Eyebrow movement: ***Task*** (no interference, right finger tapping, left finger tapping, bilateral finger tapping, volitional swallowing, reflexive swallowing).

Finger tapping: ***Task*** (no interference, contralateral finger tapping, eyebrow movement, volitional swallowing, reflexive swallowing).

Swallowing behavioural measurements, rate (number of swallows and volume per swallow), regularity, and manometric measures (amplitude and duration) data were run in separate two-way RM-ANOVAs with ***Swallowing type*** (Volitional and Reflexive) and ***Task*** (no interference, eyebrow movement, left finger tapping, right finger tapping, bilateral finger tapping) as factors.

Subject to a significant main effect, post-hoc analyses (pairwise comparisons) were performed to explore the strength of main effects and the pattern of interaction between experimental factors. When the assumption of sphericity was violated, a correction to the degrees of freedom was applied using Greenhouse- Geisser calculation. Bonferroni correction was applied on all post-hoc analyses to counteract the effect of multiple comparisons. Adjusted P values were reported when Bonferroni correction was applied. SPSS 19.0 was used with P= 0.05. Data are presented as mean ± SE unless otherwise indicated.

6.4. Results:

6.4.1 Non-swallowing motor behaviours:

6.4.1.1 *Finger Tapping Tasks:*

Rate: There were no significant main effects of ***Task*** on the rate of right finger tapping ($F_{(3,69)} = 2.30$, p = .089), left finger tapping ($F_{(2.26, 51.96)} = 1.90$, p = 0.160), bilateral finger tapping_ right finger ($F_{(1.97,45.4)} = 2.60$, p = .083) or bilateral finger tapping_ left finger ($F_{(2.36, 54.3)} = 1.40$, p = 0.260).

Regularity: There was a significant main effect of ***Task*** on the regularity of left finger tapping ($F_{(3, 69)} = 2.84$, p = .044). No further significant effects of ***Task*** on the regularity of finger tapping were identified [right finger tapping ($F_{(2.02, 46.4)} = 1.10$, p = 0.347), bilateral finger tapping_ right finger ($F_{(1.99,45.8)} = 2.80$, p = 0.073), bilateral

finger tapping_ left finger ($F_{(3, 69)} = 2.40$, $p = 0.079$)]. Bonferroni-corrected post-hoc analysis revealed no significant effects of task on the regularity of left finger tapping task $p > 0.05$.

6.4.1.2 ***Eyebrow Movement Task:***

Rate: There was a significant main effect of ***Task*** on the rate of eyebrow movements, ($F_{(5, 115)} = 19.08$, $p < 001$). Bonferroni corrected post-hoc analysis revealed that eyebrow rate was significantly decreased when paired with both swallowing tasks compared to when performed in isolation or when eyebrow movement was paired with all finger tapping tasks ($p < 0.05$) as shown in (Table 6-1).

Table 6-1: Comparisons that produced significant results during post-hoc analyses relative to the rate of eyebrow movement.

Tasks	Mean (SE)	Tasks	Mean (SE)	p
Eyebrow movement in isolation	22.667 (0.894)	Eyebrow movement paired with Reflexive swallowing	17.542 (0.862)	***< 0.001**
		Eyebrow movement paired with Volitional swallowing	18.167 (0.859)	***< 0.001**
Eyebrow movement Paired with Reflexive swallowing	17.542 (0.862)	Eyebrow movement paired with Right finger tapping	22.083 (0.938)	***0.003**
		Eyebrow movement paired with Left finger tapping	21.833 (0.902)	***< 0.001**
		Eyebrow movement paired with Bilateral finger tapping	21.75 (0.867)	***0.001**
Eyebrow movement Paired with Volitional swallowing	18.167 (0.859)	Eyebrow movement paired with Right finger tapping	22.083 (0.938)	***< 0.001**
		Eyebrow movement paired with Left finger tapping	21.833 (0.902)	***< 0.001**
		Eyebrow movement paired with Bilateral finger tapping	21.75 (0.867)	***< 0.001**

Note: The mean represents the task repetitions.

Regularity: There was a significant main effect of ***Task*** on the regularity of eyebrow movements, ($F_{(2,845,\ 78,877)} = 10.12$, $p < 001$). Bonferroni corrected post-hoc analysis revealed that eyebrow movement was significantly more variable, evident by significantly increased CV, when paired with swallowing tasks and bilateral finger tapping tasks as compared to performance in isolation ($p < 0.05$). In addition, when eyebrow movement was paired with reflexive swallowing, eyebrow movement was significantly more variable than when eyebrow movement was paired with right finger and left finger tapping ($p < 0.05$) as shown in (Table 6-2).

Table 6-2: Comparisons that produced significant results during post-hoc analyses relevant to regularity of eyebrow movement.

Tasks	Mean (SE)	Tasks	Mean (SE)	p
Eyebrow movement in isolation	18.982 (1.676)	Eyebrow movement paired with Reflexive swallowing	48.250 (5.006)	***< 0.001**
		Eyebrow movement paired with Volitional swallowing	35.617 (3.6)	***0.004**
		Eyebrow movement paired with Bilateral finger tapping	29.511 (3.313)	***0.046**
Eyebrow movement paired with Reflexive swallowing	48.25 (5.006)	Eyebrow movement paired with Right finger tapping	25.158 (2.46)	***0.008**
		Eyebrow movement paired with Left finger tapping	28.402 (2.643)	***0.039**

Note: The mean represents the CV.

6.4.2 **Swallowing Tasks:**

Rate: There was a significant main effect of ***Swallowing type*** on volume per swallow ($F_{(1,\ 23)} = 23.77$, $p< 0.001$) such that volume per swallow during volitional

swallowing (M=11.579, SE= 1.384) was significantly higher than volume per swallow during reflexive swallowing (M= 5.609, SE= 0.338, p< 0.001).

Furthermore, There was a significant main effect of ***Task*** on the rate of both swallowing tasks ($F_{(4, 92)} = 4.11$, p= 0.004) but not volume per swallow ($F_{(4, 92)} = 0.25$, p= 0.910). There was, however, no significant ***Swallowing type*** by ***Task*** interaction on the rate of swallowing ($F_{(4, 92)} = 1.56$, p= 0.193) or volume per swallow ($F_{(4, 92)} = 0.70$, p= 0.592) indicating that ***Task*** affected both types of swallowing.

Post-hoc analysis revealed that rate of swallowing was significantly lower when paired with left finger tapping (M= 6.458, SE= 0.295) than rate when swallowing was performed in isolation (M= 7.042, SE= 0.298; p= 0.009) and with bilateral finger tapping (M= 6.938, SE= 0.292; p= 0.001) (Figure 6-1).

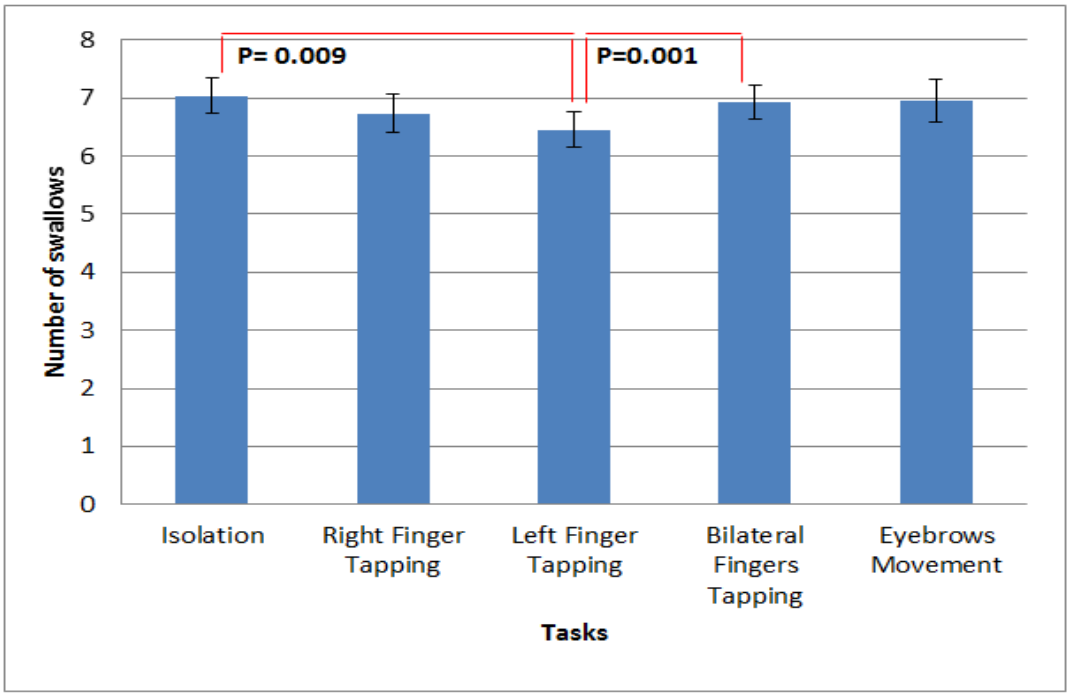

Figure 6-1: Effect of DT paradigm on the rate of swallowing from both swallowing conditions. The number of swallows in both swallowing tasks was significantly lower when paired with left finger tapping than when performed in isolation or paired with bilateral finger tapping.

Regularity: There was a significant main effect of ***Task*** on the regularity of pressure measured at the middle pharyngeal sensor ($F_{(4, 92)} = 2.95$, p= 0.024) and the UES sensor ($F_{(2.85, 65.57)} = 3.65$, p= 0.018), but not upper pharyngeal sensor ($F_{(4, 92)} = 1.81$, p= 0.135). There was, however, no significant main effect of ***Swallowing type*** on the regularity of the upper pharyngeal sensor ($F_{(1, 23)} = 1.87$, p= 0.185); middle pharyngeal sensor ($F_{(1, 23)} = 3.45$, p= 0.076) or UES sensor ($F_{(1, 23)} = 0.04$, p= 0.836). Furthermore, there was no significant ***Swallowing type*** by ***Task*** interaction on the regularity of upper pharyngeal sensor ($F_{(4, 92)} = 0.74$, p= 0.566), middle pharyngeal sensor ($F_{(2.83, 74.12)} = 0.09$, p= 0.961) or UES sensor ($F_{(4, 92)} = 0.10$, p= 0.982), indicating that ***Task*** affected the regularity of both types of swallowing.

Post-hoc analysis revealed that the CV of the middle pharyngeal sensor when swallowing was performed in isolation (M= 8.076, SEM= 0.989) was significantly lower than the CV of the middle pharyngeal sensor when swallowing was paired with left finger tapping (M= 13.941, SEM= 1.814; p= 0.020). Similarly, the CV of the UES sensor when swallowing was performed in isolation (M= 11.242, SEM= 1.694) was significantly lower than the CV of the UES sensor when swallowing was paired with left finger tapping (M= 18.537, SEM= 1.967; p< 0.001) (Figure 6-2).

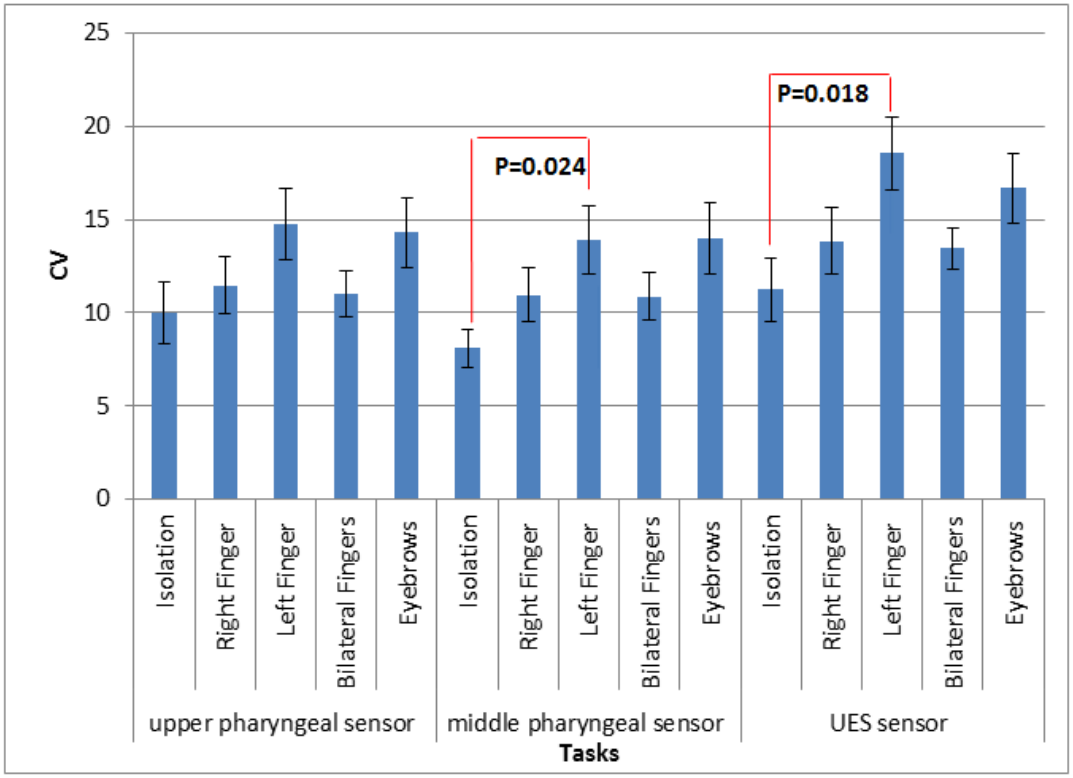

Figure 6-2: Effect of DT paradigm on the regularity of both types of swallowing.

Pharyngeal pressure amplitude measurement:

There were no significant main effects of ***Swallowing type*** on the pressure amplitude at the level of the upper pharyngeal sensor ($F_{(1, 23)}$= 2.15, p= 0.156), the middle pharyngeal sensor ($F_{(1, 23)}$= 0.89, p= 0.354) or the UES sensor ($F_{(1, 23)}$= 0.22, p= 0.641). There were also no significant main effects of ***Task*** on the pressure amplitude measured at the level of all three sensors [upper pharyngeal sensor ($F_{(1.4, 32.98)}$= 1.68, p= 0.206), middle pharyngeal sensor ($F_{(4, 92)}$= 0.82, p= 0.516) or UES sensor ($F_{(2.4, 54.12)}$= 0.56, p= 0.604)]. Furthermore, there were no significant ***Swallowing type*** by ***Task*** interactions for the pressure amplitude measures at the upper pharyngeal sensor ($F_{(1.49, 34.2)}$= 0.27, p= 0.702), the middle pharyngeal sensor ($F_{(2.4, 54.7)}$= 0.87, p= 0.443) or the UES sensor ($F_{(2.2, 50.7)}$= 0.28, p= 0.053).

Pharyngeal pressure durational measurement:

There were no significant main effects of ***Swallowing type*** on the pressure duration measured at the upper pharyngeal sensor ($F_{(1, 23)}$= 2.89, p= 0.103), the middle pharyngeal sensor ($F_{(1, 23)}$= 0.05, p= 0.819) or the UES sensor ($F_{(1, 23)}$= 0.98, p= 0.333). There were also no significant main effects of ***Tasks*** on the pressure duration measured at the upper pharyngeal sensor ($F_{(4, 92)}$= 0.84, p= 0.502), the middle pharyngeal sensor ($F_{(2.6, 59.7)}$= 2.12, p= 0.115) or the UES sensor ($F_{(4, 92)}$= 0.23, p= 0.919). Furthermore, there were no significant ***Swallowing type*** by ***Task***s interaction for the pressure duration measures [upper pharyngeal sensor ($F_{(4, 92)}$= 2.19, p= 0.076), middle pharyngeal sensor ($F_{(3.1, 70.6)}$= 0.75, p= 0.528), UES sensor ($F_{(4, 92)}$= 0.77, p= 0.551)].

6.5. **Discussion:**

This study aimed to clarify the role of M1 in pharyngeal swallowing using a DT paradigm by pairing swallowing with a competitive motor condition that activates the primary motor cortex. In addition to pairing swallowing with voluntary corticospinal finger tapping tasks, this study expanded the application of the DT paradigm by pairing swallowing with voluntary corticobulbar task of eyebrow movement. This allowed investigation of the difference between pairing tasks that utilize similar neural pathways and pairing tasks that utilize different neural pathways. Further, this study investigated the effect of the DT paradigm on two types of swallowing, volitionally and reflexively initiated swallowing. Volitional swallowing requires involvement from M1 particularly for the oral component of swallowing. Reflexive swallowing was included as the role of M1 in pharyngeal swallowing in the absence of oral manipulation is not well understood. Results from the current study indicated that the rate and regularity of eyebrow movement were significantly affected when paired with swallowing tasks, whereas rate and regularity

of both swallowing conditions were affected when paired with left finger tapping. None of the experimental conditions affected pharyngeal pressure generation.

Lack of effects of DT paradigm on finger tapping tasks:

Given their common voluntary nature, it was hypothesized that the rate and regularity of finger tapping tasks would decrease during concurrent performance of volitional swallowing and concurrent performance of voluntary eyebrow movement. However, the results did not support this hypothesis in that none of the experimental conditions affected the rate or regularity of finger tapping. These findings are in line with the findings of Daniels et al. (2006) who reported that swallowing tasks did not affect the performance of a concurrent finger tapping task. Given that finger tapping requires high input from M1 (Springer & Deutch, 1998), and M1 was found to also play a role in the execution of orofacial tasks (Avivi-Arber et al., 2011; Kern et al., 2001a; Martin et al., 2004; Sessle, 2009) and swallowing tasks (Kern et al., 2001a; Martin et al., 2004), one would expect interference during the concurrent performance of these tasks. One explanation for the lack of effect of DT on finger tapping tasks is that the functional distance between the neural areas that control these tasks within M1 may be sufficiently large to prohibit DT interference (Caroselli et al., 2006; Kinsbourne & Hicks, 1978). According to the functional cerebral space theory, the magnitude of interference between two tasks depends on the level of connection between the neural areas controlling the tasks (Caroselli et al., 2006). Even though it is acknowledged that finger tapping, eyebrow movements, and swallowing may engage M1 albeit to varying degrees, the findings of the current study support the thought that the corticospinal motor tasks tested in the current study do not share neural substrates to a significant degree with the corticobulbar motor tasks, and the areas that represent those tasks in M1 do not functionally overlap. Furthermore, descending neural pathways differ between the corticospinal and corticobulbar motor tasks resulting in minimal interference when simultaneously performing both tasks. These findings are supported by the lack of interference during the performance of two corticospinal and corticobulbar tasks such as walking

and talking or driving and talking (Pashler, 1994). In summary, the results of the current study suggest that even though the anatomical representation of the hand and facial muscles in M1 might topographically overlap, they do not functionally overlap to a significant degree. Based on the current results, tasks utilizing different neural pathways might not be the optimal choice for studies utilizing a DT paradigm to investigate neural control.

The lack of DT interference on finger tapping tasks in the present study is not in agreement with findings by Daniels et al. (2002) who reported that concurrent finger tapping rate was decreased significantly by performance of a swallowing task. The authors suggested possible overlap between the neural substrates controlling those two motor tasks. The possible overlap between the M1 neural substrates of corticospinal and corticobulbar tasks is not supported in the present research. Therefore, the reduction in finger tapping rate observed in Daniels et al. (2002) study could be due to the divided attention between the tasks, rather than overlapping between the neural substrates controlling these tasks. Differences in methodology and sample size between the two studies might explain the differences in the results. Daniels and colleagues recruited 14 participants, while 24 participants were recruited in the current study. Further, different experimental tasks were used in that cognitive and motor tasks were used in the study by Daniels and colleagues in contrast to motor tasks only in the current study. Likewise, swallowing types were different as volitionally and reflexively initiated continuous swallowing tasks were used in the current study, compared to volitional continuous swallowing only in the study by Daniels et al. (2002). A major difference as well is that Daniels and colleagues did not correct for the multiple analyses. The authors were willing to accept the inflation of the Type 1error rate given the exploratory nature of the study at that time. Bonferroni correction was applied in the current study to minimize the influence of Type 1 error in the results.

Effects of dual task on eyebrow movement:

The effects of both swallowing tasks on the rate and regularity of eyebrow movement tasks suggest functional overlapping of the neural areas controlling swallowing and eyebrow movement and further support the functional capacity sharing theory. Previous neuroimaging studies revealed substantial overlap between the neural areas controlling swallowing and orofacial motor tasks (Kern et al., 2001a; Martin et al., 2004). However, these studies did not investigate the possible neural overlap between corticobulbar and corticospinal tasks, therefore limiting the discussion to the neural control of swallowing and voluntary orofacial tasks. In addition to the functional overlap between the neural areas that control swallowing and eyebrow movement, these tasks utilize corticobulbar pathways that deliver the neural commands from the CNS system to peripheral muscles. These results revealed that pairing tasks that utilize similar neural pathways produce more apparent effects in studies utilizing a DT paradigm than pairing tasks utilizing different neural pathways or unquantifiable tasks, such as pairing cognitive with motor tasks. Future research utilizing DT paradigm should take these findings into consideration when choosing tasks to investigate neural control and lateralization of corticobulbar or corticospinal tasks.

Given that the eyebrows receive bilateral innervation from the primary motor cortex, unilateral disruption to the brain seldom disrupts eyebrow movement due to the concomitant input from the non-disrupted side (DeMyer, 1980). In addition, the eyebrow moves bilaterally, and unilateral movement of eyebrow needs extended practice to be executed. These findings suggest that eyebrow movement and swallowing share functional neural areas from both sides of M1supporting the previous reports of bilateral cortical representation of pharyngeal swallowing (Alberts, Horner, Gray, & Brazer, 1992; Daniels, Brailey, & Foundas, 1999; Daniels et al., 2002; Daniels et al., 2006; Johnson, McKenzie, & Sievers, 1993). More variability in the eyebrow movement was seen when paired with bilateral finger tapping task than eyebrow movement in isolation or when paired with unilateral finger tapping tasks. This further supports the bilateral representation of eyebrow movement in M1. This effect bilateral finger tapping on eyebrow movement regularity may be due to the overlapping of anatomical representation between finger

tapping and eyebrow movement on M1. Even though, it was postulated that these areas do not functionally overlap to a significant degree, the topographical overlap between the muscles representations of these tasks might be sufficient to disrupt the regularity of eyebrow movement but not the rate or regularity of finger tapping. The role of divided cognitive attention cannot be ruled out; however, there are no means of quantifying the effect of divided attention on the current results.

Effects of dual task on swallowing:

Significant effects of left finger tapping on the rate and regularity of both swallowing tasks were reported in the current study. Given the neural complexity of the swallowing task and the bilateral cortical activation of the swallowing musculature, it was postulated that unilateral disruption is not sufficient to disrupt the bilateral innervated process of swallowing. This was not the case in the current study. Effect of tasks on the rate of swallowing was previously described to be associated with pharyngeal phase disruption (Daniels et al., 2006).Given that left finger is mainly controlled by the right M1 (Springer & Deutch, 1998), the present finding may suggest potential right M1 involvement in the regulation of pharyngeal swallowing. In fact, previous studies have shown that right hemisphere might play a role in regulating pharyngeal swallowing (Daniels et al., 2006). The findings of possible right M1 involvement in the regulation of pharyngeal swallowing are in agreement with the clinical findings that suggest right hemisphere damage is likely to be associated with pharyngeal stage dysphagia (Daniels et al., 1996; Robbins & Levin, 1988; Robbins et al., 1993).

The effect of left finger tapping on the rate and regularity of swallowing could be due to shared mental resources between the tasks given that swallowing is a complex neuromuscular tasks and requires large mental resources (Daniels & Huckabee, 2008; Kendall et al., 2000). Left finger tapping use the non-dominant hand in right-handed individuals; therefore, it might require higher mental resources to be executed than finger tapping using the dominant hand. In fact both the left and the right hemispheres were found to be involved in the control of left hand in right-

handed subjects (Callaert et al., 2011; Davare et al., 2007; Hortobágyi et al., 2003; Perez & Cohen, 2008; Swinnen & Wenderoth, 2004). According to the "capacity sharing" theory the effect of DT task interference could be a result of sharing mental resources, or processing capacity among tasks (Kinsbourne & Hiscock, 1983; Klingberg & Roland, 1997). Therefore, when pairing swallowing with left finger tapping in right-handed individuals there may be less capacity to process each task and that would result in impairment in the performance of one or both tasks (Pashler, 1994). This assumption, however, is challenged by lack of effect of bilateral finger tapping tasks, which require higher mental resources, on the rate and regularity of swallowing, suggesting potential role of divided attention. Therefore, our data do not support the capacity sharing theory. The effect of left finger tapping on the swallowing seen in the present study might be attributed to the divided attention between the tasks.

Given that left finger tapping is not the dominant hand, one might argue that performing a task with the left hand can be considered a "novel task" for right-handed individuals; therefore, it requires higher attentional demands. Sharing the attentional demands between the left finger tapping and swallowing may have contributed to the effect on the swallowing tasks. This assumption is supported by the lack of effect of DT when swallowing was paired with the dominant right finger tapping which require less attentional demands. Similarly, lack of effect of DT on swallowing when paired with both finger tapping could be attributed to the utilization of the dominant hand to guide the performance of the non-dominant hand; therefore; reducing the attentional demand required for the bilateral finger tapping tasks. Future studies utilizing the same method might benefit from recruiting both right and left-handed individuals as well as developing a mean to quantify the contribution of divided attention to clarify this assumption. In summary, the effect of left finger tapping on the rate and regularity of the swallowing tasks may suggest potential right M1 involvement in the regulation of pharyngeal swallowing. The possible interference of shared cognitive resources and attention between the tasks should be considered when interpreting these findings. In particular, the contribution of divided attention should be considered given the complexity of the swallowing task and the novelty of

the left finger tapping for right-handed individuals. However, there is no means of quantifying the level of contribution of each of those factors in the results.

Absent effect of dual task on pharyngeal pressure generation measures:

The demonstrated lack of effect of all DT paradigms on pharyngeal pressure generation support the concept of reduced cortical involvement in the control of pharyngeal swallowing patterns (Jean, 2001; Jean & Dallaporta, 2006). Effect of DT on the rate and regularity of swallowing, but not the amplitude and duration of the pharyngeal manometry sensors are in line with the thought of involvement of M1 in the initiation of pharyngeal swallowing with reduced involvement of M1in the coordination of pharyngeal muscles (Jean, 2001; Jean & Dallaporta, 2006).

6.5.1 **Limitations:**

The level of shared attention between tasks could not be quantified in the present study or in the previous studies that investigated the effect of DT on swallowing. Therefore, the results seen in this study might be attributed to the shared attention between tasks. On the other hand, shared neural resources between tasks might have contributed to results seen in the present study. However, there is no means to quantify the level of contribution of these two factors. Future studies utilizing the same method should take into account these limitations to strengthen the results. Manipulating the complexity of the tasks might assist in quantifying attention by measuring the extent of the change in effect when more or less complex tasks are performed. In addition, future studies should recruit both right and left-handed participants to identify the potential contribution of hand dominance in the results.

6.6. **Conclusion:**

In summary, the results of the current study contribute valuable information to the neural control of swallowing and voluntary motor behaviours. Failure to detect an effect of DT interference on finger tapping tasks suggest that the neural substrates of corticospinal and corticobulbar tasks do not functionally overlap to a significant degree despite the approximate anatomical representation of the hand and face muscles in M1. Further, the effect of swallowing on the rate and regularity of the eyebrow movement suggest bilateral functional overlapping to a significant degree between neural substrates that control swallowing and orofacial muscles. These results offer partial support of bilateral representation of swallowing in the cortex. In addition, our results provide further support to the functional cerebral space model in explaining DT results. Our results further revealed potential involvement of right M1 in the regulation of pharyngeal swallowing shown by the effect of left finger tapping on the rate and regularity of swallowing. The possible interference of divided attention between tasks should be considered when interpreting these results.

The current study also contributed valuable methodological information in that pairing tasks that utilize similar neural pathways produced more apparent effects in studies utilizing DT paradigm than pairing tasks utilizing different neural pathways. Further, utilizing outcome measures that are quantifiable, such as finger tapping and swallowing, allow quantifying the effect of the tested tasks on each other unlike studies that paired motor tasks with cognitive tasks that are not quantifiable.

Chapter 7: **The effect of electrophysiological disruption to corticobulbar pathways on pharyngeal swallowing.**

7.1. **Introduction:**

As outlined in the literature review (Chapter 2), M1 plays a significant role primarily in the execution of voluntary corticospinal (Caroselli et al., 2006; Springer & Deutch, 1998) and voluntary corticobulbar tasks (Avivi-Arber et al., 2011; Kern et al., 2001a; Martin et al., 2004; Sessle, 2009). However, the involvement of this primary motor area in more complex corticubulbar tasks, such as swallowing, is not yet fully understood.

Contradictory findings were reported regarding the involvement of M1 in the regulation of pharyngeal swallowing in particular. Some studies suggested active involvement of M1 in regulating volitional swallowing related tasks, with limited involvement of M1 in regulating pharyngeal swallowing (Doeltgen et al., 2011; Huckabee et al., 2003; Kern et al., 2001a; Kern et al., 2001b; Martin et al., 2004). Other studies have suggested active involvement of M1 in the onset of pharyngeal swallowing possibly through a balance of excitatory and inhibitory mechanisms to the brainstem (Humbert, 2010; Jefferson et al., 2009; Mistry et al., 2007; Verin et al., 2012). It has been shown that changes in M1 excitability, utilizing single pulse TMS or rTMS, are functionally relevant (Humbert, 2010; Jefferson et al., 2009; Mistry et al., 2007; Verin et al., 2012), therefore targeting M1 for disruption may yield functional effects.

TMS has become widely accepted as a non-invasive method to study the changes in cortical excitability (Darling et al 2006). When utilizing this method, a magnetic impulse is discharged through an external coil held parallel to the motor cortex on the scalp. This change in magnetic field induces an electrical current in the

underlying neural tissue, and, under certain circumstances, can facilitate or inhibit excitation of the stimulated neuronal networks (Hallett, 2000). Due to its ability to manipulate neural activity to induce non-invasive transient neural disruption in conscious human volunteers, TMS is regarded as a unique research tool for investigating causal structure-function relationship (Pascual-Leone et al., 2000; Sack, 2006). This technique helps avoiding the possible contribution of divided cognitive attention in the DT paradigm results (Chapter 6) and provides more focal neural disruption. TMS induces electrical current in the underlying neural tissue, which in turn produces transient disruption in the neural activity of certain brain areas, depending on the site of stimulation. This neural disruption enables researchers to observe quantifiable changes in the performance of behaviours. For example, stimulating the area of M1 during the execution of motor behaviours may alter the excitability of neurons, which may in turn modulate the cortical motor commands producing observable behavioural effects.

Taken together, the above mentioned studies (Humbert, 2010; Jefferson et al., 2009; Mistry et al., 2007; Verin et al., 2012) provide preliminary evidence for involvement of M1 in discrete pharyngeal swallowing, based on temporal measures of swallowing onset or duration. However, to date, no investigations have been undertaken to evaluate a potential contribution of M1 motor control to pharyngeal pressure generation during swallowing. Therefore, the experiments outlined in this chapter aim to evaluate the role of M1 in reflexive and volitional pharyngeal swallowing. In line with the methodological approach of creating electrophysiological disruption of the oro-pharyngeal corticobulbar pathway (Humbert, 2010), single pulse TMS was employed to temporarily interrupt the excitability of corticobulbar and corticospinal pathways during the performance of voluntary and reflexive motor tasks.

7.2. **Hypotheses:**

Based on the findings from the above mentioned studies, the following hypotheses were tested: (These hypotheses were justified and elaborated on in hypotheses section of this thesis, Chapter3).

Hypothesis 1: Electrophysiological disruption of the dominant or non-dominant motor cortex associated with the volitional continuous swallowing will result in a significant change in rate, regularity, and volume of liquid per swallow. However there will be no significant change in pharyngeal pressure measures.

Hypothesis 2: Electrophysiological disruption of the dominant or non-dominant motor cortex associated with reflexive continuous swallowing will result in no significant change in rate, regularity, volume of liquid per swallow, and pharyngeal pressure measures.

Hypothesis 3: Electrophysiological disruption of the motor cortex associated with the voluntary corticobulbar task of jaw movement in the right or left hemispheres will result in a significant decrease in the regularity and rate of jaw movement.

Hypothesis 4: Electrophysiological disruption of the contralateral motor cortex associated with the voluntary corticospinal task of finger movement will result in a significant decrease in the regularity and rate of finger movement.

Hypothesis 5: Electrophysiological disruption of the ipsilateral motor cortex associated with the voluntary corticospinal task of finger movement will result in no significant change in the regularity and rate of finger movement.

7.3. **Methodology:**

7.3.1 **Research tasks:**

Research participants attended a single session. Following experimental set up, (refer to methodology section, Chapter 4 of this thesis), the experimental tasks were completed in randomised order. Baseline conditions consisted of performing the research tasks without experimental disruption. Research tasks included (i) finger tapping on single switch with the (i) right or (ii) left index finger, (iii) rapid up and down jaw movement, (iv) rapid volitional swallowing through a straw, and (v) rapid reflexive swallowing in response to direct injection of water to the pharynx. During the experimental conditions, corticospinal or corticobulbar pyramidal pathway excitability was interrupted by a single supra-threshold TMS pulse applied over the corresponding M1 representation of the EDM muscles for finger tapping tasks, and submental muscles group for jaw movement and swallowing tasks. Both hemispheres were investigated in counterbalanced order to control for potential order effects. All tasks were performed in randomized order for 7 sec as rapidly and consistently as possible. The procedure for each task and outcome measurements were described in detail in the methodology section of this thesis (Chapter 4).

7.3.2 **Data preparation:**

Data from the outcome measures were stored in the swallowing workstation for offline analysis. Rate was measured by counting the number of peaks produced in 7 sec. Regularity was expressed as a CV. For swallowing tasks, the number of swallows and the volume of liquid per swallow were calculated. The regularity of swallowing tasks was expressed as a CV for each of three manometry sensors. Furthermore, for swallowing tasks, the amplitude and duration of the manometry waveforms representing the pressure generated by pharyngeal muscles were also calculated from the disrupted swallows and compared to non-disrupted swallows. Detailed description of the data processing for each task is provided in the methodology section of this thesis (Chapter 4).

7.3.3 **Statistical analysis:**

RM-ANOVA was used to identify within subject differences. Rate and regularity data for non-swallowing tasks were run in two separate one-way RM-ANOVAs with ***TMS disruption*** (No disruption, Right M1 TMS, and Left M1 TMS) as a factor. Swallowing rate (number of swallows and volume per swallow) and regularity data were run in two separate two-way RM-ANOVAs with ***Swallowing Type*** (Volitional, Reflexive) and ***TMS stimulation*** (No disruption, Dominant M1 TMS, and Non-Dominant M1 TMS) as factors in each RM-ANOVA. To further explore the effect of the neurophysiological disruption, amplitude and duration of pharyngeal pressure were run in two separate three-way RM-ANOVAs with ***Swallowing Type*** (Volitional, Reflexive), ***Hemisphere*** (Dominant, Non-Dominant) and ***TMS conditions*** (Before TMS, During TMS, After TMS) as factors.

If a significant main effect was identified, post-hoc analyses (pairwise comparisons) were then performed to explore main effects and the pattern of interaction between experimental factors. When the assumption of sphericity was violated, a correction to the degrees of freedom was applied using Greenhouse-Geisser calculation. Bonferroni correction was applied to counteract the effect of multiple comparisons during post-hoc analyses. Adjusted P values were reported when Bonferroni correction was applied. SPSS 19.0 was used with P= 0.05. Data are presented as mean ± SE unless otherwise indicated.

7.4. **Results**

7.4.1 **Non-Swallowing Tasks:**

7.4.1.1 ***Finger Tapping Task:***

Rate: There was a significant main effect of ***TMS disruption*** on the rate of right and left finger tapping ($F_{(1.99,45.73)} = 8.20$, $p = .001$, $F_{(1.94,44.59)} = 17.91$, $p < 0.001$

respectively). For both left and right finger tapping, tapping rate was significantly reduced when the contralateral M1 was disrupted compared to the no disruption and ipsilateral M1 disruption, as shown in (Figure 7-1).

Regularity: There was a significant main effect of ***TMS disruption*** on the regularity of right and left finger tapping ($F_{(1.91,43.92)} = 27.56$, $p < .001$, $F_{(1.91,45.47)} = 21.55$, $p < .001$ respectively). Bonferroni corrected post-hoc analysis revealed that the CV for right finger tapping was significantly higher when the contralateral M1 was disrupted compared to the no disruption condition or ipsilateral M1 disruption. However, disruption to either hemisphere significantly decreased the regularity of the left finger tapping task as shown in (Figure 7-2).

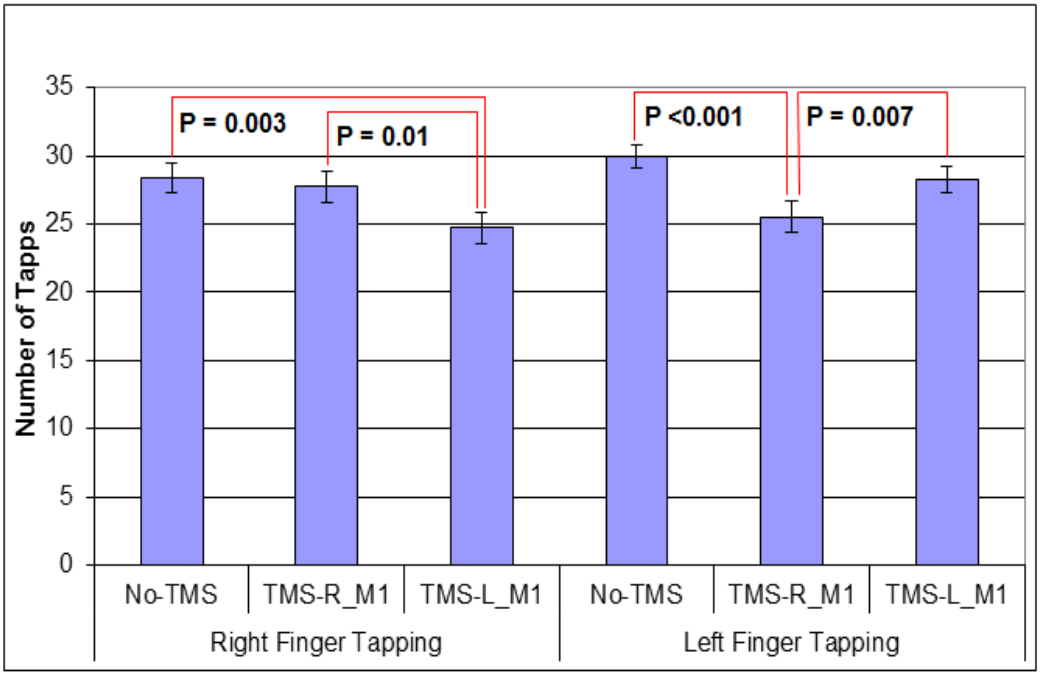

Figure 7-1: Represents the effect of TMS disruption to the corticospinal pathways on the rate of finger tapping tasks. R= Right, L= Left, M1= primary motor cortex.

7.4.1.2 ***Jaw Movement Task:***

Rate: There was no significant main effect of ***TMS disruptions*** on the rate of jaw movement ($F_{(1.49,34.35)} = 1.87$, $p = 0.18$).

Regularity: The regularity of jaw movement varied significantly with the TMS disruption conditions ($F_{(1.85,42.58)} = 23.2$, $p < .001$). Bonferroni corrected post-hoc analysis indicated that the CV was significantly higher when either the right or left hemispheres were disrupted compared to no disruption condition as shown in (Figure 7-2).

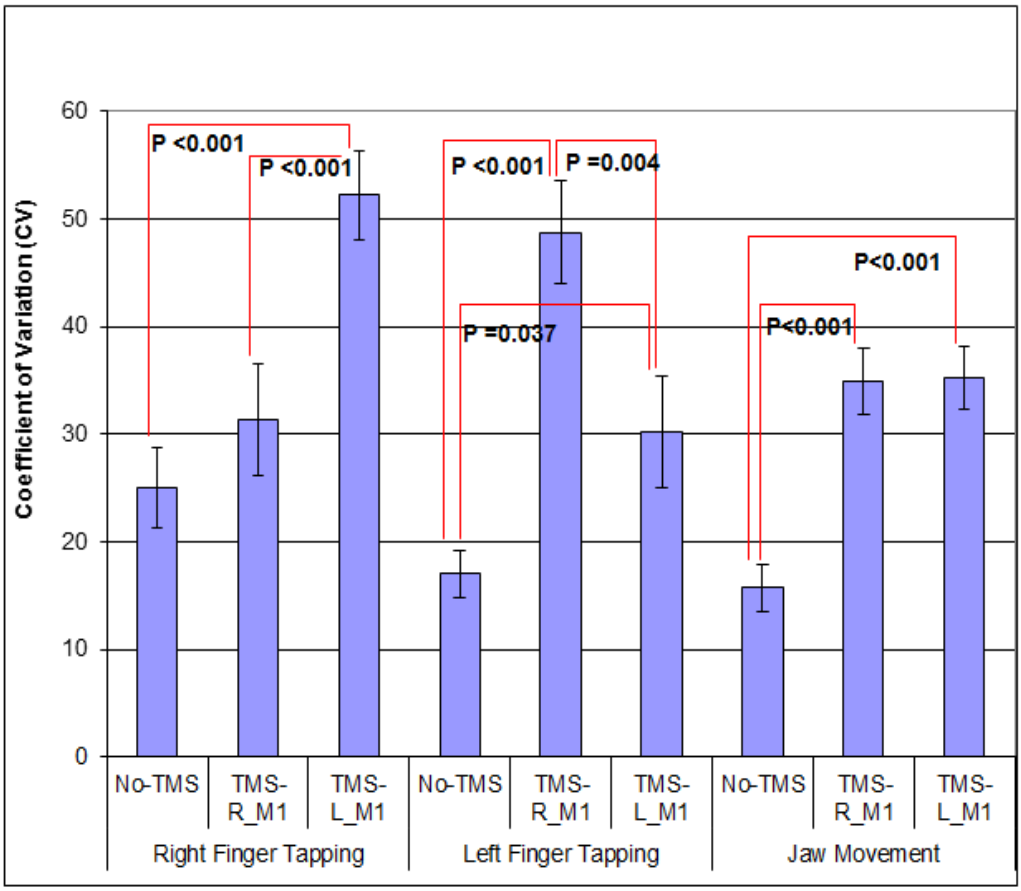

Figure 7-2: Represents the effect of TMS disruption on the regularity of non-swallowing tasks. R= Right, L= Left, M1= primary motor cortex.

7.4.1.3 ***Swallowing Tasks:***

Rate: There were significant main effects of ***Swallowing type*** on number of swallows ($F_{(1, 23)} = 5.35$, p= 0.03) and volume per swallow ($F_{(1,23)} = 18.28$, p< 0.001). Bonferroni corrected post-hoc analysis revealed that number of swallows during volitional swallowing (M= 7.444, SE= 0.358) was significantly higher than number of swallows during reflexive swallowing (M= 6.653, SE= 0.338, p = 0.03). Volume per swallow during volitional swallowing (M=10.236, SE= 1.201) was significantly higher than volume per swallow during reflexive swallowing (M= 5.580, SE= 0.382, p< 0.001). There were no significant effects of ***TMS stimulation*** on the number of swallows or volume per swallow. ($F_{(2,46)} = 0.34$, p= 0.714; $F_{(2,46)} = 0.03$, p= 0.970, respectively). In addition there were no significant ***Swallowing type*** by ***TMS stimulation*** interactions for the number of swallows ($F_{(2,46)} = 0.910$, p= 0.410) or volume per swallow ($F_{(2,46)} = 0.527$, p= 0.594).

Regularity: TMS stimulation produced significant main effects on the regularity of pressure at the upper pharyngeal sensor ($F_{(2, 46)} = 4.04$, p= 0.024), middle pharyngeal sensor ($F_{(2, 46)} = 4.35$, p= 0.019) and UES sensor ($F_{(1.46, 33.46)} = 4.34$, p= 0.032). There was, however, no significant effect of ***Swallowing type*** on the regularity of pressure at any sensor [upper pharyngeal sensor ($F_{(1,23)} = 0.06$, p= 0.809), middle pharyngeal sensor ($F_{(1,23)} = 0.23$, p= 0.639) or UES sensor ($F_{(1,23)} = 0.02$, p= 0.899)]. Likewise there was no significant ***Swallowing type*** by ***TMS stimulation*** interaction for the regularity of pressure generation at the upper pharyngeal sensor ($F_{(2, 46)} = 0.36$, p= 0.699), middle pharyngeal sensor ($F_{(2, 46)} = 0.34$, p= 0.714) or UES sensor ($F_{(2, 46)} = 0.73$, p= 0.488) suggesting effect of ***TMS stimulation*** on the regularity of both swallowing tasks.

Bonferroni corrected post-hoc analysis indicated that the CV for upper pharyngeal sensor was significantly lower during the no disruption condition (M = 11.220, SE = 0.843) compared to when TMS was applied over the dominant M1 (M = 15.994, SE = 1.298; p = 0.004). Further, the CV for the middle pharyngeal sensor was significantly higher when the dominant M1 was disrupted (M = 16.606, SE = 1,315) compared to the no TMS disruption condition (M = 11.595, SE = 0.901; p =

0.010). Likewise, the CV of UES sensor was significantly higher when the dominant M1 was disrupted (M = 17.135, SE = 0.859) than no TMS disruption condition (M = 12.786, SE = 0.863; p = 0.002) as shown in (Figure 7-3). There was, however, no significant difference in CV between no disruption condition and non-dominant M1 disruption, or between non-dominant M1 disruption and dominant M1 disruption p > 0.05.

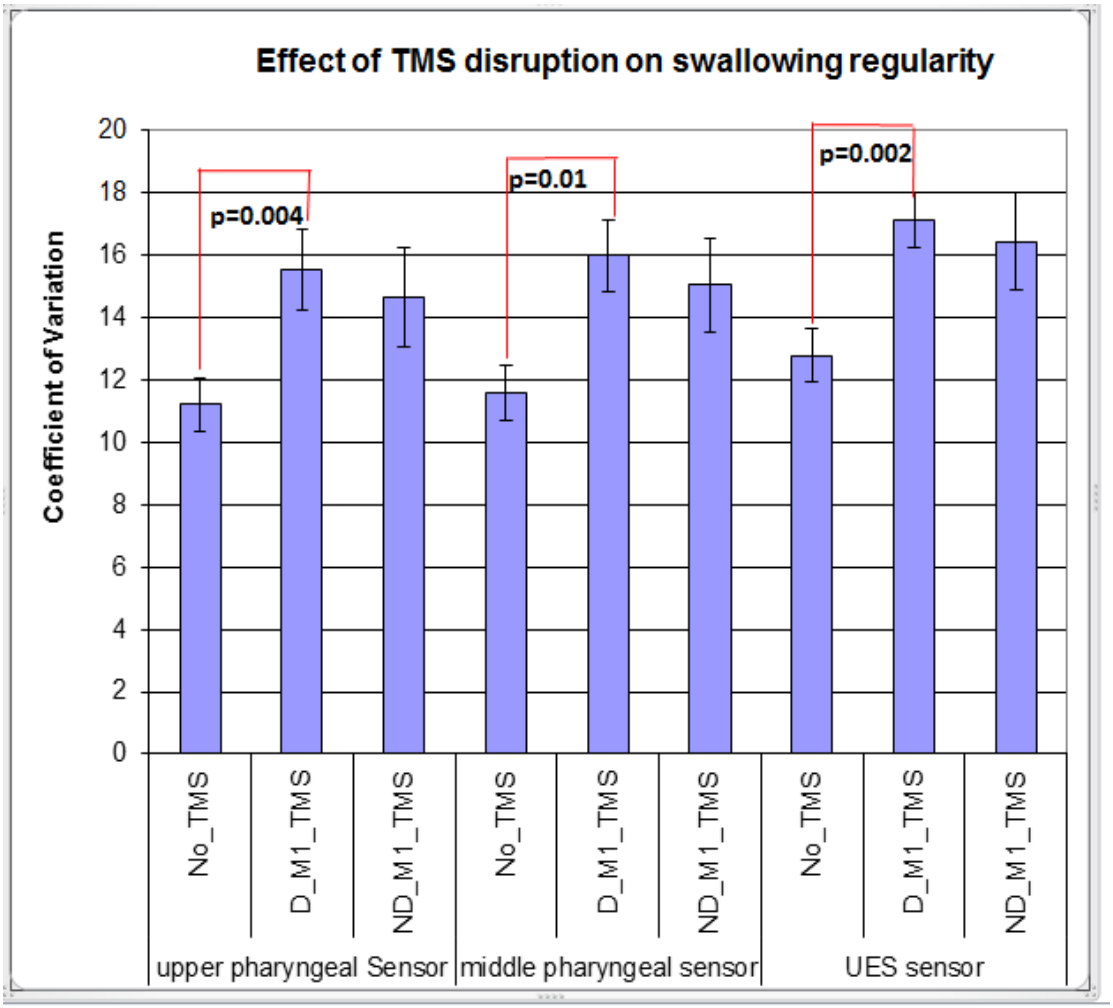

Figure 7-3: represents the effect of TMS stimulationon the regularity of both swallowing tasks. D= Dominant, ND= Non-dominant, M1= Primary motor cortex.

7.4.2 **Effects of electrophysiological disruption on pharyngeal pressure during volitionally and reflexively initiated pharyngeal swallowing:**

7.4.2.1 ***Pharyngeal pressure durational measurement:***

TMS conditions produced significant main effects on the duration of pressure at the UES sensor ($F_{(2,46)} = 4.94$, $p = .011$) and total duration of pressure ($F_{(2, 46)} = 4.22$, $p = .021$). Furthermore, there was a significant ***Swallowing type*** by ***TMS conditions*** interaction for pressure duration at upper pharyngeal sensor ($F_{(2,46)} = 4.12$, $p = .023$). There were however, no significant effects of ***Swallowing type***, ***Hemisphere***, ***Swallowing type*** by ***Hemisphere*** interaction, or ***Swallowing type*** by ***Hemisphere*** by ***TMS conditions*** interaction on the duration of pressure for any of the sensors $p > 0.05$ as shown in (Table 7-1).

Bonferroni corrected post-hoc analysis revealed that for both swallowing conditions the duration of pressure at UES sensor was significantly longer during TMS disruption (M = .704, SE = .024) than before TMS disruption (M = .670, SE = .026; p = .040). Similarly total duration of pressure was significantly longer during TMS disruption (M = .704, SE = .024) than before TMS disruption (M = .671, SE = .026; p = .040). Furthermore, during volitional swallowing, duration of pressure at upper pharyngeal sensor during TMS disruption (M= 0.325, SE= 0.02) was significantly longer than after TMS disruption (M= 0.302, SE= 0.017; p= 0.038).

7.4.2.2 ***Pharyngeal pressure amplitude measurement:***

There were no significant main effects of ***Swallowing type***, ***Hemisphere***, or ***TMS conditions***, or interaction between these factors on the amplitude of pressure recorded by the manometry sensors $p > 0.05$ as shown in (Table 7-2).

Table 7-1: The effect of Swallowing Type, Hemisphere, TMS Conditions and the interaction between those factors on pharyngeal pressure duration across the 3 manometric sensors.

Within-Subject Factors	Measures	df	F	P
Swallowing type	Upper pharyngeal Sensor_ D	(1,23)	3.259	0.08
	Middle pharyngeal Sensor_D	(1,23)	1.003	0.33
	UES Sensor_D	(1,23)	0.047	0.83
	Total-D	(1,23)	0.510	0.48
Hemisphere	Upper pharyngeal Sensor_ D	(1,23)	0.157	0.70
	Middle pharyngeal Sensor_D	(1,23)	1.000	0.33
	UES Sensor_D	(1,23)	0.162	0.69
	Total-D	(1,23)	1.100	0.31
TMS disruption	Upper pharyngeal Sensor_ D	(2,46)	1.579	0.22
	Middle pharyngeal Sensor_D	(1,23)	0.994	0.33
	UES Sensor_D	(2,46)	4.936	***0.01**
	Total-D	(2,46)	4.223	***0.02**
Swallowing Type * Hemisphere	Upper pharyngeal Sensor_ D	(1,23)	4.069	0.06
	Middle pharyngeal Sensor_D	(1,23)	3.259	0.08
	UES Sensor_D	(1,23)	0.415	0.53
	Total-D	(1,23)	0.055	0.82
Swallowing Type * TMS disruption	Upper pharyngeal Sensor_ D	(2,46)	4.124	***0.02**
	Middle pharyngeal Sensor_D	(1,23)	0.993	0.33
	UES Sensor_D	(2,46)	2.492	0.09
	Total-D	(2,46)	0.423	0.66
Hemisphere * TMS disruption	Upper pharyngeal Sensor_ D	(2,46)	0.406	0.67
	Middle pharyngeal Sensor_D	(1,23)	0.996	0.33
	UES Sensor_D	(2,46)	0.038	0.96
	Total-D	(2,46)	0.662	0.52
Swallowing Type * Hemisphere * TMS disruption	Upper pharyngeal Sensor_ D	(2,46)	0.249	0.78
	Middle pharyngeal Sensor_D	(1,23)	1.002	0.33
	UES Sensor_D	(2,46)	0.445	0.64
	Total-D	(2,46)	0.357	0.70

*Note: D= Duration. P=0.05. *Represents significant values.*

Table 7-2: The effect of Swallowing Type, Hemisphere, TMS Conditions and the interaction between those factors on pharyngeal pressure amplitude across the 3 manometric Sensors.

Within-Subject Factors	Measures	df	F	P
Swallowing type	Upper pharyngeal Sensor_ Peak	(1,23)	0.004	0.95
	Middle Pharyngeal Sensor_ Peak	(1,23)	2.447	0.13
	UES Sensor_ Peak	(1,23)	1.256	0.27
Hemisphere	Upper pharyngeal Sensor_ Peak	(1,23)	3.488	0.06
	Middle Pharyngeal Sensor_ Peak	(1,23)	1.918	0.18
	UES Sensor_ Peak	(1,23)	0.026	0.87
TMS disruption	Upper pharyngeal Sensor_ Peak	(2,46)	0.680	0.51
	Middle Pharyngeal Sensor_ Peak	(2,46)	2.243	0.12
	UES Sensor_ Peak	(2,46)	0.288	0.75
Swallowing Type * Hemisphere	Upper pharyngeal Sensor_ Peak	(1,23)	0.002	0.96
	Middle Pharyngeal Sensor_ Peak	(1,23)	0.055	0.82
	UES Sensor_ Peak	(1,23)	0.693	0.41
Swallowing Type * TMS disruption	Upper pharyngeal Sensor_ Peak	(2,46)	0.568	0.57
	Middle Pharyngeal Sensor_ Peak	(1.29,29.65)	0.575	0.50
	UES Sensor_ Peak	(2,46)	2.336	0.11
Hemisphere * TMS disruption	Upper pharyngeal Sensor_ Peak	(2,46)	0.052	0.95
	Middle Pharyngeal Sensor_ Peak	(2,46)	0.691	0.51
	UES Sensor_ Peak	(2,46)	0.615	0.55
Swallowing Type * Hemisphere * TMS disruption	Upper pharyngeal Sensor_ Peak	(2,46)	0.705	0.50
	Middle Pharyngeal Sensor_ Peak	(2,46)	0.430	0.65
	UES Sensor_ Peak	(2,46)	0.698	0.50

Note: P=0.05.

7.5. **Discussion:**

This study evaluated the role of M1 in pharyngeal swallowing and voluntary corticobulbar and corticospinal behaviours of varying complexity by measuring the effects of electrophysiological disruption of corticobulbar and corticospinal pathways

excitability on the performance of motor behaviours. Hemispheric TMS disrupted rate and regularity of finger tapping tasks and regularity of jaw movement and swallowing tasks. In addition, hemispheric TMS produced significant effects on the duration but not the amplitude of the pharyngeal pressure in particular during the volitional swallowing task.

Effect of M1 disruption on the rate and regularity of finger tapping tasks:

Experimental neural disruption or strokes that affect M1 were found to produce significant effects on the corticospinal musculature due to the active involvement of M1 in the control of corticospinal motor tasks (Springer & Deutch, 1998; Van Den Berg et al., 2011). In fact, hemiplegia is one of the common symptoms of strokes affecting M1, given that most corticospinal muscles are controlled by the contralateral hemisphere. Therefore, it was not surprising that TMS disruption to the representation of the hand muscles on the contralateral M1 reduced the rate and regularity of finger tapping task in the current study. Strong contralateral activation of M1 during the finger movement tasks was reported by neuroimaging studies (Gerloff et al., 1998d; Müller et al., 2000; Pollok et al., 2003; Pollok et al., 2004) and neurophysiologic studies (Gerloff et al., 1997; Gerloff et al., 1998c; Kopp et al., 2000). Disruption in the regularity of finger tapping in response to contralateral M1 disruption by single pulse TMS was also reported during a complex finger tapping task in right-handed participants (Chen et al., 1997). Our data suggested that the discharge of TMS over the EDM muscle representation on M1 altered the excitability of the stimulated area (Hallett, 2000). This alteration in cortical excitability might have modulated the motor plan of finger movement causing the observed reduction in the rate and regularity of finger tapping. The results of the current study provide further support to the feasibility of single pulse TMS as neural disruption tool to investigate corticospinal tasks.

Interestingly, TMS disruption of left M1 in the current study resulted in disruption of the regularity of movement in the ipsilateral hand as well as the contralateral hand. This finding suggests possible involvement of the left hemisphere

in controlling motor tasks performed by hand regardless of which hand was used. Similar results were reported by imaging studies investigating neural control of complex finger tapping tasks in right-handed subjects in that the left hemisphere showed larger activation during left hand movement than right hemisphere activation during right hand movement (Hayashi et al., 2008; Verstynen et al., 2005). These findings were confirmed by studies utilizing single pulse TMS to disrupt M1 motor control during a complex finger tapping task in right-handed participants (Chen et al., 1997). Disruption in the timing of finger movement was observed when TMS was applied over the ipsilateral hemisphere, which was particularly evident during left hemispheric interruption. These studies recruited right-handed participants only; therefore, these results might reflect increased neural resources when performing tasks with the non-dominant left hand. Studies recruiting right and left handed participants are needed to clarify these results.

Effect of M1 disruption on the rate and regularity of jaw movement task:

Creating neurophysiological disruption to the area of M1 controlling the jaw movement task produced a reduction in the regularity of the movement. During jaw opening, M1 may play a role in sending excitatory neural commands to activate the jaw opening muscles and inhibitory neural commands to inhibit the jaw closing muscles, and the opposite occurs for jaw closing (Bass & Morrell, 1992; Perlman & Christensen, 1997). Modulating the excitability of submental muscles representation on M1 by TMS in the current study might have altered the balance of excitatory and inhibitory motor commands from M1 to the target muscles producing observed reduction in the regularity of the movement.

The findings of the present study further support the previous findings of direct M1 involvement in the control of voluntary corticobulbar tasks. M1 has been identified to play a major role in the planning and initiation of voluntary orofacial movements as M1 was activated regularly during execution of voluntary corticobulbar tasks (Malandraki et al., 2009; Sessle et al., 2007; Shibusawa et al., 2009). These results were further supported by findings from neurophysiological

studies utilizing single pulse TMS as MEPs were frequently detected with higher amplitude during volitional contraction of the submental muscle group compared to swallowing tasks (Doeltgen et al., 2011).

The executions of voluntary corticobulbar movements, such as tongue movements, were found to yield bilateral activation in a number of neural areas, in particular M1 and S1 (Kern et al., 2001a; Martin et al., 2004). However, one could argue that this bilateral activation is due to the bilateral muscle contraction during the performance of orofacial tasks. If this was the case, unilateral cortical lesions would result in severe effects and might abolish the execution of orofacial movements such as jaw movement. However, unilateral lesions above the level of the trigeminal nerve were not found to yield obvious weakness of jaw motion, suggesting strong symmetrical bilateral innervation of jaw movement muscles (Bhatnagar, 2001). The effect of TMS disruption to the M1from either hemisphere on the regularity of jaw movement observed in the present study confirms the previous reports of bilateral cortical innervation to orofacial muscles (Avivi-Arber et al., 2010a; Grinevich et al., 2005; Haque et al., 2010; Hatanaka et al., 2005; Lund & Kolta, 2006b; Sessle, 2009).

Lack of hemispheric dominance was reported previously in studies utilizing TMS to elicit MEP from the masseter muscle (Ortu et al., 2008) and the mylohyoid muscle (Hamdy et al., 1996). In addition, neuroimaging studies revealed symmetrical neural activation during voluntary oral structure movement compared to volitional and reflexive swallowing muscles (Dziewas et al., 2003), suggesting less hemispheric lateralization during the execution of orofacial movements. Therefore, the findings of this study provide further support to the symmetrical bilateral representation of voluntary corticobulbar tasks in M1, in particular tasks that involved the masseter and the mylohyoid muscles. Stimulation to either hemisphere yielded similar effects on the regularity of jaw movement.

The observed lack of effect of TMS disruption to either right or left M1 on the rate of jaw movement could be attributed to the fact that disruption in this study was unilateral; therefore, it may not have been sufficient to affect the rate of the movement due to the concomitant input from the non-disrupted hemisphere. It may

further be possible that M1 contributes to the initiation and the timing of the rhythmical corticobulbar movement, with the rest of the movement pattern controlled by motor neuron pools below the cortex. This assumption is supported by the ability of decerebrate animals to produce a rhythmic chewing reflex (German, Crompton, & Thexton, 2009; Thexton, Crompton, Owerkowicz, & German, 2009). Furthermore, lesions involving face M1 in animals altered but did not diminish rhythmic chewing tasks (Hiraba et al., 2007; Yamamura et al., 2002). The disruption to M1 in the present study might have altered the planning and initiation process producing the observed effects in the regularity of the movement.

One could argue that the degree of neural disruption of the single pulse TMS used in the present study was not sufficient to produce long lasting disruption. Single pulse TMS produce transient disruption; therefore, it might not be sufficient to produce a long lasting disruption that could affect the execution of bilaterally innervated corticobulbar tasks. Further studies utilizing other neural disruption mechanisms such as rTMS would clarify this ambiguity in the results. In addition, further studies utilizing bilateral neural disruption mechanisms would add to the understanding of the bilateral control of voluntary corticobulbar tasks.

Effect of M1 disruption on the rate and regularity of swallowing tasks:

The effect of TMS disruption to the submental muscles representation on M1 from the dominant hemisphere on the regularity of volitionally and reflexively initiated swallowing supports the concept of possible involvement of M1 in the regulation of pharyngeal swallowing. The data of the present study provide further support to the existence of hemispheric dominance in the control of swallowing in humans. One possible explanation for the effect of M1 disruption on the regularity of swallowing is that M1 sends motor commands to the swallowing CPG to initiate swallowing when sensory information from the peripheral swallowing sensors breaches a certain threshold. TMS disruption, however, might have transiently altered these motor commands; therefore, the regularity of swallowing during TMS disruption was reduced. This hypothesis is supported by findings from previous

studies utilising TMS to disrupt the pharyngeal muscles representation on M1, where a delay in initiation of swallowing (Humbert, 2010; Verin et al., 2012) or rapid onset of swallowing (Jefferson et al., 2009; Mistry et al., 2007) was observed. Further, electromagnetic studies in animals revealed dense connections between the primary motor cortex and the DSG in the brainstem (Jean & Car, 1979). However, if M1is strongly involved in initiating pharyngeal swallowing, one would expect an effect on the number of swallows given the results of the above studies. This was not evident in the current study.

A lack of effect of TMS disruption on the overall number of swallows during the volitional and reflexive swallowing conditions could be attributed to the transient disruption in this study, as TMS disruption was delivered with 2 sec interval during the execution of the task. This might not be sufficient to significantly disrupt the flow of the task and reduce the number of swallows or volume per swallow. It is postulated that even though the cortical input to the CPG was transiently disrupted, the continuous sensory input during continuous swallowing was sufficient to trigger irregular swallowing events from the CPG. This assumption is supported by the ability of decerebrate animals to swallow (German et al., 2009; Thexton et al., 2009). These assumptions, however, need to be clarified by clearer outcome measures such as combined manometry and VFSS, which would allow for observation of the pattern of movement and also biomechanical changes during disruption. In addition, utilizing or longer lasting disruption methods such as rTMS might help clarifying these assumptions. The results of the current study, however, provide further support to the feasibility of single pulse TMS to modulate cortical input during the performance of motor behaviour. This provides further support to the ability of this tool to investigate a causal relationship.

Some studies revealed that neural disruption induced by TMS may not be restricted to the stimulation site, but also modulates neural activity in remote or inter-connected cortical and subcortical areas to a lesser degree (Bestmann et al., 2005; Denslow et al., 2005; Pleger et al., 2006). However, the largest effect of TMS on neural activity was found to occur at the stimulated area (Sarfeld et al., 2011; Wassermann et al., 1996). In addition, the figure-of-8 coil used in the current study

offers a relatively localized site of activation with less penetration depth of the electrical field due to their relatively smaller wings (Nollet, Van Ham, Deprez, & Vanderstraeten, 2003). Therefore, it is safe to speculate that the behavioural changes seen in the present study are due mainly to the neural modulation induced at the stimulated area.

Effect of M1 disruption on the pharyngeal pressure measures during swallowing:

The TMS disruption of the submental muscles representation on M1 in the present study produced significant increase in the duration, but not the amplitude of pharyngeal pressure. Data revealed that the pressure duration of the upper pharyngeal sensor was significantly longer during the TMS disruption than after the TMS disruption in volitional swallowing but not the reflexive swallowing condition. One explanation for these findings is that TMS disruption during volitional swallowing produced an effect on the voluntary oral movement, in particular tongue movement. The base of tongue lowers and retracts to meet the posterior pharyngeal wall during the initiation of pharyngeal swallowing. During this movement, the tongue may contact the upper pharyngeal sensor. Providing TMS disruption to M1 may have modulated the motor plan and therefore resulted in longer base of tongue to posterior pharyngeal wall approximation. This explanation is supported by lack of effect of TMS disruption on the duration of the upper pharyngeal sensor during reflexive swallowing task where tongue movement was minimised by the dental bite-block and instruction to minimize tongue movement during the task. These results support the thought of active involvement of M1 in the regulation of voluntary swallowing related motor tasks associated with the oral phase of swallowing (Doeltgen et al., 2011; Huckabee et al., 2003; Jean, 2001; Jean & Dallaporta, 2006; Kern et al., 2001a; Martin et al., 2004).

Results also revealed a small but statistically significant increase in the duration of UES relaxation during TMS disruption than before the disruption. This increase in UES opening was found in both volitionally and reflexively initiated swallowing tasks. It was suggested that M1 modulate the swallowing CPG plan

through excitatory or inhibitory mechanisms (Mistry et al., 2007). Disruption to the representation of submental muscles on M1 in the current study might have altered these cortical mechanisms producing observable increase in the duration of pharyngeal pressure. The increased duration of UES opening during TMS disruption may suggest that more inhibitory neural commands were sent to the cricopharyngeus muscle, hence the extended relaxation of the otherwise contracted cricopharyngeus muscle (Ertekin & Aydogdu, 2003). Similarly, significant increase in the total duration of pressure in the pharynx was observed during TMS disruption than before the disruption during the performance of both volitionally and reflexively initiated swallowing tasks. This increased in total duration might be caused by the increased in duration of the upper pharyngeal sensor during volitional swallowing and the duration of UES relaxation during both swallowing tasks as a result of TMS disruption. It is hypothesized that the increased duration of pharyngeal pressure generation is a result of TMS modulation of cortical motor commands to the CPG. However this assumption must remain speculative due to the absence of direct evaluation of brainstem responses.

The TMS disruption to M1 in the current study did not affect the amplitude of the pharyngeal pressure. Lack of effect of TMS disruption on the level of pharyngeal muscle contraction might be due to the concomitant input from the non-disrupted hemisphere given that swallowing is bilaterally represented in the brain (Hamdy et al., 1999a; Hamdy et al., 1999b; Mosier et al., 1999a). Another possible explanation is that single pulse TMS produces transient disruption that might not be long enough to produce significant effects to a tightly controlled motor behaviour process such as swallowing. Therefore, providing single pulse TMS to the area of M1 may have altered some aspects of this process due to transient nature of stimulation of this tool. Further studies utilizing longer lasting disruption mechanisms such as rTMS are warranted to verify this assumption.

Stimulation of the dominant hemisphere was found to affect the regularity of swallowing in the current study; however, stimulation to either hemisphere yielded similar effects on the duration of pharyngeal pressure generation. These findings suggest bilateral and symmetrical cortical control of pharyngeal muscle contraction

during swallowing. These results may suggest that hemispheric dominance might be specific to different components of swallowing with some components having more equally distributed hemispheric control mechanisms (Daniels et al., 2006). One might argue that pharyngeal swallowing initiation is controlled by the dominant hemisphere, whereas pharyngeal muscle contraction in the ensuing swallow requires bilateral innervation due to the complexity of this patterned movement. In fact, less lateralization was reported during reflexive swallowing tasks compared to volitional swallowing tasks suggesting stronger bilateral representation of the pharyngeal phase of swallowing (Dziewas et al., 2003; Furlong et al., 2004; Martin et al., 2004; Michou & Hamdy, 2009).

7.6. **Conclusion:**

Taking the above findings together, results revealed that modulating the excitability of muscle representations on M1 affected the performance of corticobulbar and corticospinal motor tasks. During the execution of various motor behaviours, M1 sends motor commands, based on the peripheral sensory information, to the respective cranial or spinal nuclei to facilitate the execution of movements. Providing TMS stimulation to the representation of specific muscles on M1 alters the excitability of the neurons at the stimulated area. This modulation of the cortical excitability may either alter the cortical motor commands from M1 or initiate a competitive descending volley to the muscle of interest producing observable behavioural effects. On this note providing TMS stimulation to M1 in the present study produced observable behavioural effects, albeit to varying degrees, during the execution of a number of motor behaviours of varying complexity.

The results from the current study support the concept of active involvement of contralateral M1 in the execution of voluntary corticospinal motor tasks, as well as bilateral M1 involvement in the control of voluntary orofacial tasks. Moreover, these data suggest M1 involvement in the control of pharyngeal swallowing in that M1

plays a role in modulating the swallowing plan at the swallowing CPG possibly through a balance of excitatory of inhibitory mechanisms.

Hemispheric lateralization of function was evident in the corticospinal tasks as effects were observed mainly when the contralateral hemisphere was stimulated. In contrast, effects in regularity of jaw movement were observed when either of the hemispheres were stimulated suggesting symmetrical cortical representation of orofacial muscles. Disruption to the dominant hemisphere only affected the regularity of swallowing, with no observed effects when the non-dominant hemisphere was stimulated suggesting hemispheric dominance in the control of some aspects of swallowing. In contrast, our data suggested possible symmetrical cortical representation in the control pharyngeal pressure during swallowing. Disruption to either hemisphere increased the duration of pharyngeal pressure during both swallowing tasks, suggesting that the lateralization is likely to be specific to some swallowing components, with certain components such as patterned pharyngeal musculature movement, being more bilaterally organized due to its complexity.

Chapter 8: **Pharyngeal pressure differences between four conditions of swallowing in healthy participants.**

8.1. **Introduction:**

As outlined in the literature review (chapter 2), in most studies of neural control of swallowing, tasks included primarily discrete water or saliva swallows (Murguia et al., 2009). This is a methodological limitation in the current knowledge given that ingestive liquid swallowing frequently consists of multiple consecutive swallows. The behavioural and mechanical differences of discrete and continuous liquid swallowing using cup drinking (Chi-Fishman & Sonies, 2000) and straw drinking (Daniels et al., 2004; Daniels & Foundas, 2001) were investigated utilizing VFSS. Results indicated that continuous swallowing requires higher neuromuscular demands to accommodate the increased flow rate when compared to discrete swallowing. Chi-Fishman and Sonies (2000) reported that most deglutitive event durations were significantly shorter during sequential swallowing compared to discrete swallowing as faster movements were required in continuous swallowing. However, the authors reported longer duration during pharyngeal transit, which they attributed to hypopharyngeal bolus containment during sequential swallowing. VFSS, however, does not provide quantitative data about the pharyngeal and UES pressure generation mechanisms during swallowing.

Pharyngeal manometry is a tool used to measure the strength and duration of pharyngeal pressure with excellent temporal resolution (Butler et al., 2009). It has been used to study the effects of rehabilitation techniques on pharyngeal pressure (Bulow, Olsson, & Ekberg, 1999; Doeltgen, Witte, Gumbley, & Huckabee, 2009; Witte et al., 2008), although discrete saliva and water swallows were used in these studies. Pharyngeal manometry has also been utilized to investigate pressure differences between discrete saliva and discrete water swallows (Castell et al., 1990;

Cerenko et al., 1989; Olsson et al., 1995; Perlman et al., 1993). Castell et al. (1990) reported reduced pressure duration during saliva swallowing. However, the opposite was found by Perlman et al. (1993) with no differences in pharyngeal pressure amplitude. Saliva swallowing, in addition, produced lower nadir pressure in the UES (Olsson et al., 1995), as well as longer UES opening (Cerenko et al., 1989). A recent study by Witte et al. (2008) revealed that saliva swallows were produced with significantly higher peak amplitude at the upper pharyngeal sensor only and significantly longer pressure duration at the upper pharyngeal and middle pharyngeal sensors compared to discrete water swallows. Bolus volume has been identified to affect the pharyngeal pressure generation in that lower pharyngeal pressure and lower duration are needed for boluses with bigger volumes (Butler et al., 2009).

People frequently drink continuously during the ingestion of liquids; therefor, comprehensive evaluation of swallowing types is warranted to understand how different swallowing types may affect pharyngeal pressure. This knowledge will enable clinicians and researchers to differentiate between normal and abnormal swallowing and ultimately could be used to guide swallowing rehabilitation. Further, if the manometric measures of individuals with disordered swallowing are to be compared to those of normal swallowing a more comprehensive data about different swallowing types are needed.

The aim of this study was to identify the pharyngeal pressure differences between discrete and continuous swallowing. It was hypothesized that there would be significant differences in pharyngeal pressure generation between discrete saliva, discrete water, volitional continuous water, and reflexive continuous water swallowing. This hypothesis was elaborated in the hypotheses section of this thesis (Chapter 3). Specifically, it is hypothesised that:

- Higher peak amplitude for discrete saliva swallowing will be evident when compared to discrete water and continuous water swallowing.
- No significant difference will be measured in peak amplitude between discrete water swallowing and continuous water swallowing.

- Longer duration of pressure will be generated during discrete saliva and water swallowing compared to continuous water swallowing.
- Longer duration of pressure will be generated during discrete saliva swallowing compared to discrete water swallowing.

8.2. Methods:

8.2.1 Research Tasks:

Participants completed five blocks of trials of four swallowing tasks in randomized order. In each block of trials, participants performed volitional continuous swallowing for 7 seconds, reflexive continuous swallowing for 7 seconds, five discrete saliva swallows and five discrete 10 ml water swallows. Pharyngeal pressure was measured during task execution using intra-luminal manometry. Measures extracted from the manometric data included: (1) maximum amplitude (mmHg) for all sensors and (2) duration (msec) of the pressure generated by each sensor and the total duration. The procedure for each task and outcome measurements were described in detail in the methodology section of this thesis (Chapter 4).

8.2.2 Data preparation:

Given that the first and the last swallows of continuous swallowing conditions are considered discrete swallows (Chi-Fishman & Sonies, 2000; Daniels & Foundas, 2001), they were excluded from the analysis. Therefore, the three swallows following the first swallow in the sequence were extracted during the continuous swallowing tasks. The amplitude and duration of pharyngeal pressure were calculated. To match the number of swallows for each task, the middle three swallows of the discrete swallowing conditions (saliva and water) were also extracted and prepared for analysis. Fifteen swallows from each swallowing type were averaged and prepared for data analysis. A detailed description of the data processing for each task is provided in the methodology section of this thesis (Chapter 4).

8.2.3 **Statistical analysis:**

RM-ANOVAs were used to identify within subjects differences. The manometric measures of amplitude and duration of pharyngeal pressure were run in two separate one-way RM-ANOVAs with ***Swallowing type*** (Discrete water swallows, Discrete saliva swallows, Volitional continuous swallowing, Reflexive continuous swallowing) as a factor.

When a significant main effect was present, post-hoc analyses (pairwise comparisons) were then performed to explore the strength of the main effects and the pattern of interaction between experimental factors. When the assumption of sphericity was violated, a correction to the degrees of freedom was applied using Greenhouse- Geisser method. Bonferroni correction was applied to counteract the effect of multiple comparisons during post-hoc analysis. Adjusted P values were reported when Bonferroni correction was applied. SPSS 19.0 was used with a priori significance level set at P= 0.05. Data are presented as mean ± (SE) unless otherwise indicated.

8.3. **Results:**

8.3.1 **Amplitude of pharyngeal pressure:**

There were no significant effects of ***Swallowing type*** on the pressure amplitude at the upper pharyngeal sensor ($F_{(1.5, 35.43)} = 0.62$, $p = 0.504$). However, there were significant main effects of ***Swallowing type*** on the pressure amplitude at middle pharyngeal sensor ($F_{(2.1, 48.3)} = 4.02$, $p = 0.023$) and UES sensor ($F_{(3, 69)} = 20.11$, $p < 0.001$). Mean peaks and nadir amplitudes (and SE) for all sensors across swallowing conditions are displayed in Table 8-1.

Bonferroni-corrected post-hoc analyses revealed that there were no significant differences in pressure amplitude at the middle pharyngeal sensor across the

swallowing types (p> 0.05). Furthermore, Bonferroni-corrected post-hoc analyses showed that nadir pressure at UES sensor during discrete saliva swallowing was significantly lower than during volitionally initiated continuous swallowing (p<0.001), reflexively initiated continuous swallowing (p< 0.001) and discrete water swallowing (P= 0.042). In addition, discrete water swallowing produced significantly lower nadir pressure than volitionally initiated continuous swallowing (p= 0.025) and reflexively initiated continuous swallowing (p= 0.006).

Table 8-1: Mean (and SE) peak amplitude and nadir pressure in (mmHg) across the sensors and swallowing types.

Swallowing Type	**Upper pharyngeal Sensor**	**Middle Pharyngeal Sensor**	**UES Sensor**
Volitional continuous Swallowing	104.130 (7.974)	92.212 (6.790)	-3.672 (1.001)
Reflexive continuous swallowing	108.824 (16.882)	98.293 (4.867)	-2.516 (1.109)
Discrete saliva Swallowing	119.417 (7.567)	114.471 (8.214)	-9.905 (1.054)
Discrete water swallowing	103.931 (5.913)	102.620 (7.171)	-6.294 (0.999)

8.3.2 **Duration of pharyngeal pressure:**

There were significant main effects of ***Swallowing type*** on the pressure duration at upper pharyngeal sensor ($F_{(3, 69)} = 26.15$, $p< 0.001$), the middle pharyngeal sensor ($F_{(2.1, 49.02)} = 4.13$, $p = 0.020$), the UES sensor ($F_{(2.2, 49.5)} = 4.60$, p

=0.013) as well as total duration ($F_{(2.2, 50.5)} = 4.95$, $p = 0.009$). Descriptive statistics for the duration of pressure generation are displayed in Table 8-2.

Post-hoc analyses revealed that saliva swallowing produced longer duration at the level of the upper pharyngeal sensor than discrete water swallowing ($p<0.001$), volitional continuous swallowing ($p<0.001$) and reflexive continuous swallowing ($p<0.001$). In addition, the pressure duration at the middle pharyngeal sensor during discrete saliva swallowing was significantly longer than the duration of pressure at the middle pharyngeal sensor during reflexive continuous swallowing ($p= 0.024$). The pressure duration at the middle pharyngeal sensor during discrete saliva swallowing was not significantly different from volitional continuous swallowing ($p= 0.121$) or discrete water swallowing ($p= 0.152$).

Post-hoc analyses revealed that the duration of the UES opening during discrete water swallowing was longer than during reflexive continuous swallowing ($p= 0.023$) and during discrete saliva swallowing ($p= 0.003$). However, the UES opening duration during discrete water swallowing was not significantly different from volitional continuous swallowing ($p= 0.131$).

Similar to the duration of UES opening, post-hoc analysis revealed that the total duration of the swallow during discrete water swallowing was significantly longer than during reflexive continuous swallowing ($p= 0.024$) and during discrete saliva swallowing ($p= 0.006$), but not significantly different from total duration during volitional continuous swallowing ($p= 0.131$).

Table 8-2: Mean (and SE) pressure duration in (msec)) across sensors and across swallowing types and total duration across swallowing types.

Swallowing Type	**Upper Pharyngeal Sensor**	**Middle Pharyngeal Sensor**	**UES Sensor**	**Total Duration**
Volitional continuous Swallowing	0.302 (0.015)	0.256 (0.022)	0.779 (0.037)	0.789 (0.037)
Reflexive continuous swallowing	0.311 (0.018)	0.256 (0.015)	0.768 (0.029)	0.771 (0.029)
Discrete saliva Swallowing	0.418 (0.019)	0.324 (0.023)	0.805 (0.033)	0.810 (0.033)
Discrete water swallowing	0.324 (0.015)	0.270 (0.029)	0.892 (0.045)	0.902 (0.048)

8.4. **Discussion:**

This study is the first to document the pharyngeal pressure differences between discrete and continuous swallowing. These findings contribute valuable information to the swallowing literature as few studies have investigated the biomechanical differences between discrete and continuous liquid ingestion. Comprehensive evaluation of swallowing types is warranted to understand how these may affect pharyngeal pressure. This knowledge will assist clinicians and researchers in identifying the pharyngeal pressure differences between normal and abnormal swallowing in different swallowing types and ultimately guide their rehabilitation decisions.

Effects of swallowing type on amplitude of pharyngeal pressure:

The present study revealed higher nadir pressure at UES sensor during water swallowing than during saliva swallows. This elevated nadir pressure during water swallowing could be attributed to the intra-bolus pressure applied into the lower sensor when water boluses pass through the UES. In fact, significant lower nadir pressure during saliva swallowing when compared to discrete water swallowing has been previously reported (Olsson et al., 1995).

In addition, nadir pressure during discrete water swallows was lower than during continuous swallowing. The continuous flow of water during continuous swallowing applies continuous intra-bolus pressure on UES sensor therefore might have elevated the nadir pressure recording during the continuous swallowing tasks. Other explanation might be that the UES opening during discrete swallows would likely generate some degree of suction force due to increased pressure in the pharynx and negative pressure at the UES as it opens (McConnel et al., 1988). The UES contraction, however, is likely to be incomplete during the continuous swallowing conditions; therefore generating less of a suction force as the UES rapidly re-opens for the consecutive swallows.

Our data did not reveal any differences of pharyngeal pressure amplitude across swallowing types, which is in agreement with previous research comparing the pharyngeal pressure differences between discrete water and saliva swallowing (Castell et al., 1990; Perlman et al., 1993). Due to the lower volume and higher viscosity of saliva than water, one would expect saliva to require greater effort than water to be cleared from the pharynx. This assumption is supported by previous findings from Witte et al. (2008) who reported higher pharyngeal pressure in the upper pharyngeal sensor during discrete saliva swallowing compared to discrete water swallowing. The authors attributed the change to increased involvement of the tongue to drive the saliva compared to water swallows. The findings from Witte et al. (2008) are different from the findings of the present study which did not report higher amplitude at the upper pharyngeal sensor during saliva swallowing. The authors in the study by Witte et al. (2008) compared effortful and non-effortful discrete saliva

and water swallowing. Therefore, that might have influenced the results when comparing the bolus type (saliva vs. water) without the manoeuvre.

In summary, our data revealed that discrete water swallowing produced lower nadir pressure at UES sensor than continuous water swallowing. In addition, bolus type influenced the nadir pressure of the UES sensor in that saliva swallowing produced lower nadir pressure than water swallowing. This may be attributed to intra-bolus pressure applied by the water boluses during water swallowing conditions. A study with combined VFSS and manometry is warranted to evaluate the level of intra-bolus pressure interference in the pharyngeal pressure generation across swallowing types.

Effects of swallowing type on the duration of pharyngeal pressure:

Duration of pressure at the upper pharyngeal sensor, the middle pharyngeal sensor, the UES sensor, and the total duration of the pressure generation was affected by swallowing types in the current study. The duration of pressure at the upper and middle pharyngeal sensors during saliva swallowing was longer than during water swallowing. Similar findings were reported by Witte et al. (2008) and Perlman et al. (1993).This could be attributed to the slower flow rate of saliva compared to water as the volume of saliva is lower than that of water in the current study. Butler et al. (2009) reported a decrease in pharyngeal pressure duration with increased volume of swallowed boluses. The weight, velocity and the gravity factors may have contributed to faster transition of the heavier water bolus through the pharynx.

Interestingly, the opening duration of the UES and the total duration of pressure generation during discrete water swallowing were significantly longer than the discrete saliva swallowing. One would expect saliva swallowing to produce significant longer total duration given its slower flow rate. This was not the case in the present study. A possible explanation could be that the volume of discrete water bolus is larger than saliva, therefore required wider opening of the UES, hence the longer duration to close. An increase in bolus volume was found to increase the

duration of UES relaxation, suggesting that UES opening duration is sensitive to volume change (Butler et al., 2009).

The duration of UES opening and total duration during discrete water swallowing were also significantly longer than during reflexively induced continuous swallowing. The participants had no control over the flow rate during the reflexive swallowing condition. This might have caused the participants to rapidly open and close the UES to accommodate for the fast flow rate of the water, thereby shortening UES opening and the total duration time. This has been observed in the studies investigating the differences between discrete and continuous water swallowing using VFSS as rapid elevation and lowering of hyolaryngeal movement, which links directly to opening and closing of the UES, was observed during volitional continuous swallowing (Chi-Fishman & Sonies, 2000; Daniels & Foundas, 2001). It is postulated that rapid hyolaryngeal movement was faster during the reflexive swallowing task compared to the discrete water swallowing condition. A study utilizing manofluorography is warranted to confirm this assumption as it will allow direct observation of hayolaryngeal movement and UES opening and closing.

In summary, discrete water swallows were found to produce longer UES opening compared to continuous water swallowing, in particular reflexive continuous swallowing. This decrease in pharyngeal pressure duration could be due to the faster reaction of pharyngeal muscles to adapt for the fast flow of water during continuous water swallowing. This was particularly evidenced during reflexive swallowing due to the lack of voluntary control over the bolus.

Bolus type was also found to influence pharyngeal pressure duration measures as longer duration of upper and middle pharyngeal sensors was identified during saliva swallowing compared to water swallowing. The lower volume and higher viscosity of saliva may have contributed to the increased duration of saliva clearance from the pharynx. These differences in pharyngeal pressure between swallowing and boluses types should be taken into consideration when assessing or designing rehabilitation programmes for patients with dysphagia.

8.5. **Conclusion:**

Pressure generation mechanisms differ between swallowing types and boluses types. Our results confirm prior research that reports saliva produced longer pharyngeal duration and lower nadir pressure than water swallows. More critically, a discrete water bolus tends to require longer time to pass through the UES compared to saliva swallowing or continuous water swallowing where participants are required to react faster to adapt for the continuous flow rate of water. A study with combined VFSS and manometry is required to further clarify the results and help quantifying the effect intra-bolus pressure on the pharyngeal pressure generation measures.

Part V: Discussion

Chapter 9: **Discussion**

This research programme provides valuable information about the role of M1 in pharyngeal swallowing. To understand the role of M1 in swallowing, comparative tasks that require high input from M1, voluntary corticobulbar and corticospinal tasks were used as reference tasks to evaluate the more reflexive tasks of volitionally and reflexively initiated pharyngeal swallowing. The contribution of M1 in swallowing was investigated in two main studies, both of which evaluated swallowing parameters during neural disruption conditions. Two neural disruption techniques were used: DT paradigm and single pulse TMS. Results from both studies revealed potential involvement of M1 in the regulation of pharyngeal swallowing, reflected in increased irregularity and decreased rate of swallowing. In addition, utilizing single pulse TMS over the submental muscles representation on M1 affected the duration of pharyngeal pressure. The findings of this research programme have also provided further support to the previous findings of strong contralateral M1 involvement in the regulation of corticospinal tasks, as well as active bilateral M1 involvement in the control of voluntary corticobulbar tasks.

The findings of this research programme have also provided methodological contribution. Performing multiple trials of tasks in a single session did not affect the performance of voluntary corticospinal and corticobulbar tasks nor the complex corticobulbar tasks of swallowing. These results suggest that the effects seen in the experimental studies were the result of experimental manipulation.

As a secondary aim of this research programme, this project was the first to investigate the pharyngeal pressure differences between discrete and continuous swallowing. Pressure generation mechanisms were found to differ between swallowing types and boluses types, providing new insights to the biomechanics of swallowing.

9.1. Methodological considerations:

This research programme provided a number of methodological contributions that will be discussed in details below.

9.1.1 Effect of trials on task performance:

This research programme investigated the consistency with which corticobulbar and corticospinal motor behaviours were performed within a single research session (Chapter 5). Performing multiple trials of tasks within-session did not significantly influence any of the evaluated measures.

Most healthy subjects have the ability to learn new skills or improve existing skills given the opportunity to practice (Lee et al., 2010). Frequent repetitions of tasks during a session may yield changes in the performance, due to factors such as practice or fatigue; however, this was not evident in the current study. A number of factors may have contributed to the lack of effect of trials on the evaluated measures. The lack of effect of trials on the rate and regularity of finger tapping tasks could be due to the simplicity of the tapping tasks as participants were instructed to use index fingers to tap on single switch. Previous research, however, indicated increased cortical excitability as evidenced by increased MEP amplitude recorded from the extensor pollicic brevis muscle following repeated thumb abduction (Bütefisch et al., 2000). It was not clear from this report, however, if there was change in the associated peripheral performance. The high repetition of the thumb abduction task might have increased the demand on the cortical system; therefore, the increase in cortical excitability might have been an adaptation mechanism for the rapid repetition of the task rather than reflecting change in the peripheral performance. Cortical excitability was not measured in the current study, limiting direct comparison of these results.

Similarly, repetitions of tasks within-session were not sufficient to produce an effect in the performance of eyebrow movement and jaw movement tasks. The simplicity of the movement, unidirectional up and down movement, might not have been sufficient to pose a challenge to the corticobulbar system, thus hindering the

potential detrimental effects of factors such as fatigue or practice. In addition, most voluntary corticobulbar tasks require bilateral muscle activation to be executed; therefore, they are less prone to be affected by factors such as fatigue or practice in the absence of excessive task repetitions.

Lack of influence of task repetitions on the rate and regularity of volitionally and reflexively initiated pharyngeal swallowing could be due to the high frequency of performance of this task in everyday life. However, performance of 200 discrete water swallows, at a rate of one swallow every five seconds was found to alter the cortical excitability as evident by increased MEP amplitude from the pharyngeal muscles (Fraser et al., 2003). No functional changes have been reported as a result of the alteration of cortical excitability, therefore this increase in cortical excitability might have been an adaptation of the neural system to the increased frequency of task performance to ensure consistency of performance in the increased demand from the peripheral system. Previous findings from our lab supports this assumption as repetition of discrete swallowing - 60 swallows at rate of a swallow every at least 10 seconds- did not produce effects on corticobulbar excitability when participants were given longer time to prepare for the subsequent swallows (Al-Toubi et al., 2011). Due to the unnatural method for initiating the reflexive swallowing task in the current research programme, one might argue that this task is not performed in everyday life and thus represents a novel task for which a practice effect might influence task performance. The documented lack of a repetition effect on the outcomes measures related to the reflexive swallowing task may be due to the more reflexive nature of this phase of swallowing, with reduced cortical involvement (Jean, 2001; Jean & Dallaporta, 2006). This is further supported by the lack of effect of swallowing tasks repetitions on the pharyngeal pressure generation mechanisms.

In summary, repetition of tasks in a single session did not affect the performance of voluntary corticospinal and corticobulbar tasks. Even though prior studies reported that high repetitions of tasks was found to alter cortical excitability, no functional changes were reported in those studies, possibly suggesting that the alteration of cortical excitability might be an adaptation mechanisms to the increasing demand on the system. Therefore, it is safe to speculate that trials have minimal, if

any, effect in the results of studies utilizing experimental manipulation of motor behaviours.

9.1.2 **Dual-Task paradigm:**

Previous studies have utilized DT paradigm to investigate the neural organization of swallowing (Daniels et al., 2002; Daniels et al., 2006). These studies have contributed to the understanding of hemispheric organization of swallowing; however, some methodological limitations were identified in particular utilizing non quantifiable tasks, or pairing tasks that utilize different neural pathways. The current study addressed these limitations and utilized motor tasks that were quantifiable. Utilizing quantifiable tasks have allowed accurate measurement of the effects of each task on the concurrently performed task; therefore, increasing confidence in the results of DT paradigm on task performance. In addition, the current study further utilized motor tasks that share similar neural pathway, such as swallowing and eyebrow movement, to provide clearer representation of task prioritization and competition for resources within the hemisphere, cortical region and neural pathways. This provided an opportunity to investigate the functional contribution of specific brain area, i.e. M1, in the execution of motor behaviour, rather than limiting the investigation to the hemispheric lateralization of the tasks. The current study further utilized a reflexive swallowing and compared effects of the DT paradigm on volitional swallowing to effects of DT paradigm on reflexive swallowing. Investigating both types of swallowing facilitated the identification of the role of the cortex, M1, in the control of pharyngeal swallowing.

Future studies utilizing DT paradigm may benefit from utilizing quantifiable tasks that share similar neural pathways, in particular when investigating the role of particular neural area. A major limitation in utilizing DT paradigm is the difficulty to quantify the divided attention between tasks. Future studies utilizing this behavioural method should find means of quantifying divided attention to increase confidence of the results.

9.1.3 **Biomechanical differences between discrete and continuous swallowing:**

To our knowledge, this programme is the first to assess the pharyngeal pressure differences between discrete and continuous swallowing; therefore, providing a methodological contribution to the literature. Four swallowing types were investigated in the current study which were, discrete saliva, discrete water, volitional continuous and reflexive continuous swallowing. Pressure generation mechanisms differed between swallowing types and boluses types. Swallowing types produced observable differences on the pressure generation at the level of the UES in particular in that discrete swallowing produced lower nadir pressure at UES compared to continuous swallowing. The UES contracted after each swallow during discrete swallowing tasks; therefore, allowing for build-up of pressure in the pharynx during swallowing. As the UES opens it creates a suction force due to increased pressure in the pharynx and negative pressure at the UES level. In contrast, UES contraction during continuous swallowing may be incomplete due to rapid opening and closing to accommodate for the increased flow rate. Therefore, less of a suction force may be created at the level of the UES during continuous swallowing. This decrease in suction force may have contributed to the elevation of nadir pressure during continuous swallowing. Given the higher suction force at the UES level during discrete swallowing, it might be a better option during liquid ingestion for patients with pharyngeal muscles weakness. Another possible explanation for elevated nadir pressure during continuous swallowing is that continuous flow of water applies continuous intra-bolus pressure on UES. However, studies utilizing manofluorography are needed to clarify this assumption as it is hard to infer intra-bolus pressure without direct viewing the bolus position.

In addition to swallowing type, bolus type was also found to affect nadir pressure, in that saliva swallows produced lower nadir pressure at UES compared to water swallows. Intra-bolus pressure applied to the UES sensor when water boluses passes through the UES may have elevated the nadir pressure during water swallows.

In fact, previous studies documented significant lower nadir pressure during saliva swallows when compared to discrete water swallows (Olsson et al., 1995). Studies investigating the UES function during swallowing should attempt to quantify intra-bolus pressure utilizing manofluorography.

Swallowing type and bolus type were also found to affect the pharyngeal pressure duration in that discrete swallowing produced longer pharyngeal pressure duration than continuous swallowing. In fact, decreased pharyngeal pressure duration was reported during the ingestion of heavier boluses (Butler et al., 2009). Weight, velocity and gravity factors may have contributed to faster transition of the heavier water boluses through the pharynx. In addition the fast flow of water boluses in the continuous swallowing condition has contributed the decreased duration of pharyngeal pressure in particular during reflexive swallowing task. Interestingly, the duration of the UES sensor, and the total duration of pressure generation during discrete water swallows were significantly longer than the reflexive pharyngeal swallowing, and discrete saliva swallows and tendency towards longer duration when compared to continuous volitional water swallowing task as shown in (Table 8-2). Given the slower flow rate of saliva, one would expect saliva swallows to produce longer total duration. This was not the case in the present study as discrete water bolus took longer time to pass through the UES compared to saliva. Increased bolus volume was found to increase the duration of UES relaxation (Butler et al., 2009). Given the sensitivity of UES to volume change, the volume of discrete water bolus is larger than saliva, therefore required wider opening of the UES, hence the longer duration to close. This assumption however was not true for continuous water swallowing where larger volumes were ingested than discrete water swallows. The duration of UES opening and total duration during discrete water swallows were significantly longer than during continuous reflexive swallowing. In the reflexive swallowing tasks participants had no control over the flow rate of water. This lack of control may have caused rapid opening and closing of the UES to accommodate for the flow rate of the water, thereby shortening UES opening and the total duration time. These findings further suggest that discrete boluses are a better method of liquid

ingestion than continuous swallowing in particular for patients with pharyngeal muscles weakness.

Bolus type has also influenced the duration of pharyngeal pressure generation. Saliva was found to produce longer pharyngeal pressure duration at the level of the upper and middle pharyngeal sensors. The lower volume and the higher viscosity of saliva have resulted in slower flow rate of saliva compared to water producing longer duration. Similar findings were reported by Witte et al. (2008) and Perlman et al. (1993) in that significantly longer pressure durations were observed during discrete saliva swallows compared to discrete water swallows. Given the above findings, heavier cohesive boluses might be suitable for patients with delayed pharyngeal swallowing, or weaker pharyngeal muscles with normal UES as bolus will depend mainly on weight, gravity and velocity to move through the pharynx. Larger discrete boluses of water might be more suitable than continuous water swallowing for patients with pharyngeal phase dysphagia, as discrete water boluses were found to produce the longest UES opening therefore allowing for bolus clearance. A study utilizing combined manometry and VFSS is warranted to confirm these assumptions.

These findings contribute valuable information to the swallowing literature as limited number of studies investigated the biomechanical differences between discrete and continuous liquid ingestion. Comprehensive evaluation of swallowing types is warranted to understand how different swallowing types may affect pharyngeal pressure. This knowledge will assist clinicians in and researchers identifying the pharyngeal pressure differences between normal and abnormal swallowing in different swallowing types and ultimately guide their decisions.

9.2. **Implications on the neural control of motor behaviours:**

In addition to the methodological contribution, this research programme also contributed to the understanding of neural control of corticospinal and corticobulbar

motor behaviours. As each motor behaviour warrants various considerations, they will be addressed separately.

9.2.1 Implications on the neural control of corticospinal motor tasks:

The effects of creating electrophysiological disruption to the hand M1 on the rate and regularity of contralateral hand movement confirm previous reports of substantial involvement of M1 from the contralateral hemisphere during the performance of voluntary corticospinal tasks (Springer & Deutch, 1998; Van Den Berg et al., 2011). Similar results were reported by Chen et al. (1997) in that disruption of contralateral hand M1 affected the regularity of a complex hand movement task in right-handed participants. These data suggest that TMS modulated the motor commands from the contralateral M1 to the target muscle. Interestingly, our results revealed an effect of the left hemisphere disruption on the regularity of the ipsilateral hand movement as well as the contralateral hand. These findings are in line with previous assumptions of involvement of the left hemisphere in controlling corticospinal motor tasks regardless of which hand was used (Hayashi et al., 2008; Verstynen et al., 2005). The left hand was the non-dominant hand for participants in the current study; therefore, higher mental resources and cognitive attention were likely required to perform tasks with this hand. This is supported by previous reports of left hemisphere involvement in controlling the left hand in right-handed subjects (Callaert et al., 2011; Davare et al., 2007; Hortobágyi et al., 2003; Perez & Cohen, 2008; Swinnen & Wenderoth, 2004).

The hand muscles and facial muscles representation on M1 might topographically overlap; however, our data revealed that the neural substrates of hand and orofacial movements do not functionally overlap. This assumption is evidenced by lack of DT paradigm interference on the performance of finger tapping tasks when paired with swallowing and eyebrow movement. These results suggest that the functional distance between the neural areas that control these tasks within M1 may

be sufficiently large to prohibit DT interference (Caroselli et al., 2006; Kinsbourne & Hicks, 1978). In addition, different neural pathways are utilized to carry neural commands from the CNS to the peripheral muscles when performing hand movements and orofacial movements; therefore, DT may interfere less than previously thought. These findings provide further support to the functional cerebral space theory that indicates the magnitude of interference between two tasks depends on the level of connection between the neural areas controlling the tasks (Kinsbourne & Hicks, 1978). Based on the current results, tasks utilizing different neural pathways might not be the optimal choice for studies utilizing DT paradigm to investigate neural control.

9.2.2 **Implication on the neural control of voluntary corticobulbar movements:**

The current results support previous findings of active involvement of M1 in the regulation of voluntary orofacial movement (Avivi-Arber et al., 2011; Kern et al., 2001a; Martin et al., 2004; Sessle, 2009). Disruption of face M1 from either hemisphere utilizing single pulse TMS affected the regularity of the jaw movement task suggesting equal representation of voluntary orofacial movements in both hemispheres. In fact, past research identified bilateral activation of number of cortical areas, in particular M1 and S1, during the performance of tongue movement task (Kern et al., 2001a; Martin et al., 2004). One might argue that the bilateral cortical activation during orofacial movement might be due to the fact that bilateral muscle activation is required to execute orofacial movements. If this was the case, unilateral or bilateral neural disruption would have produced significant effects on the execution of orofacial movements. However, unilateral lesions above the level of trigeminal nerve was not found to cause obvious weakness on jaw motion (Bhatnagar, 2001). In addition, it has been previously documented that most CNs related to the orofacial musculature receive bilateral input from the cortex (Bhatnagar, 2001). The fact that neural disruption to either hemisphere in the current

research programme altered the orofacial movement provides further evidence to the bilateral representation in of orofacial musculature in the cortex.

As previously discussed, in chapter 7, our data suggest a lack of hemispheric dominance in the control of orofacial musculature as similar effect on the regularity was observed when stimulating either hemisphere. These results are in agreement with the previous findings of lack hemispheric dominance in the control of masseter muscle (Ortu et al., 2008) and mylohyoid muscle (Hamdy et al., 1996). In addition, neuroimaging studies revealed symmetrical neural activation during voluntary oral structure movement compared to volitional and reflexive swallowing muscles (Dziewas et al., 2003) suggesting less hemispheric lateralization during the execution of orofacial movements. Therefore, the findings of this study provide further support to the symmetrical bilateral representation of voluntary corticobulbar tasks in M1, in particular tasks that involved masseter and mylohyoid muscles such as jaw opening and closing.

Given the symmetrical bilateral representation of orofacial muscles in the cortex, it is suggested that unilateral disruption to face M1 may not alter orofacial movements to a significant degree. This assumption is supported by lack of significant effect of TMS disruption to the submental muscles representation on M1 on the rate of jaw movement tasks. This reduced effect of TMS disruption on the rate may be due to possible concomitant input from the undisrupted hemisphere. Another possible explanation is that M1 is involved in the planning and initiation of rhythmic orofacial movement with the rest of the process controlled by the motor neuron pools below the cortex. This assumption is supported by the ability of decerebrate animals to produce rhythmic jaw movement (German et al., 2009; Thexton et al., 2009). Therefore, TMS disruption might have modulated the planning and initiation of the jaw movement at the level of M1 producing observable effect in the regularity of the movement. Studies utilizing bilateral stimulation mechanisms are warranted to verify these assumptions.

Pairing voluntary orofacial eyebrow movement with *bilateral* finger tapping task altered the regularity of rhythmic orofacial movement. However, pairing

eyebrow movement with *unilateral* finger tapping did not induce any effects on the rate and regularity of either task. These results further support the bilateral M1 involvement in regulating orofacial movements. However, these findings are contradictory to the above mentioned finding that unilateral TMS disruption to M1 disrupts the regularity of orofacial movement. This could be due to the less focal disruption of DT paradigm to the neural substrates in M1 compared to TMS. In addition, reduced functional overlapping between hand muscles and orofacial muscles representation on M1 may have contributed to the reduced effect of unilateral finger tapping on eyebrows movement. The anatomical representation of the hand and the eyebrows overlap on M1, however, they may be functionally distinct. This topographical overlap between the muscles representations of hand and eyebrows may be sufficient to disrupt the regularity of eyebrow movement when both hands were utilized, but not sufficient to affect the rate or regularity of finger tapping. The role of divided cognitive attention should be considered when interpreting these results. The current findings indicate that single pulse TMS provided more focal disruption of M1 than DT paradigm, hence the difference in the findings between the two disruption methods.

The rate and regularity of eyebrow movement were affected when paired with swallowing tasks suggesting greater functional overlapping between the neural areas that control those tasks. The findings of the current research confirm previous neuroimaging findings of substantial overlap between the neural areas controlling swallowing and orofacial motor tasks (Kern et al., 2001a; Martin et al., 2004). In addition to the shared neural substrates, these tasks utilizing similar neural pathways to deliver neural commands from the CNS to the peripheral muscles. Therefore, these tasks competed for resources from the neural areas and neural pathways producing observed effects on the rate and regularity of eyebrows movement. These findings provide further support to the functional cerebral space theory (Kinsbourne & Hicks, 1978).

It was suggested in chapter 7 that unilateral disruption may not be sufficient to disrupt the rate of orofacial movement due to the concomitant input from the undisrupted hemisphere. Given that swallowing is bilaterally represented in the brain

(Alberts et al., 1992; Daniels et al., 1999; Daniels et al., 2002; Daniels et al., 2006; Johnson et al., 1993), the fact that swallowing reduced the rate and regularity of the eyebrow movement when tasks were performed concurrently provides further support to bilateral innervation of orofacial movement. Given the bilateral innervation of swallowing and eyebrows movement, one would expect diminish performance of one or both tasks when paired together given the competition for resources from both hemispheres. However, this bilateral disruption of face M1was sufficient to alter, but not diminish, the rate and regularity of the eyebrow movement suggesting possible involvement of other subcortical neural areas in controlling rhythmic orofacial movements. In fact, decerebrate animals were found to produce rhythmic jaw movement (German et al., 2009; Thexton et al., 2009). These findings suggest that M1 may play an active role in regulating voluntary orofacial movements; however, some aspects of these movements are controlled by subcortical areas.

9.2.3 **Implications for the neural control of swallowing:**

The current research programme extends the knowledge of the involvement of M1 in regulating pharyngeal swallowing. A potential more active role of right M1than left M1 in controlling pharyngeal swallowing was identified in the study implementing the DT paradigm. The rate and regularity of swallowing were reduced when paired with the left finger tapping task, which is mainly controlled by the right M1. Clinical findings suggested that right hemisphere damage is associated with pharyngeal phase dysphagia, providing further support to the role of right M1 in regulating pharyngeal swallowing (Daniels et al., 1996; Robbins & Levin, 1988; Robbins et al., 1993). The findings of the effect of DT paradigm on swallowing are contradictory to the previously discussed findings of lack functional overlapping between the neural areas of hand and swallowing in M1. Therefore, the possibility of divided attention on the result of the DT paradigm study in the current project should be considered when interpreting these results. The participants were all right-handed; therefore, performing tasks with the non-dominant left hand requires higher attentional demands and mental resources. In fact, previous studies identified a

contribution from both hemispheres when performing tasks with the non-dominant left hand in the right-handed population hemisphere (Callaert et al., 2011; Davare et al., 2007; Hortobágyi et al., 2003; Perez & Cohen, 2008; Swinnen & Wenderoth, 2004). The shared attention between the complex swallowing task and the non-dominant left finger task could have caused the decrease in rate and regularity of swallowing. This assumption is supported by the lack of effect of DT paradigm on swallowing when paired with the dominant right finger tapping, or bilateral finger tapping. In the case of bilateral finger tapping, the performance of non-dominant hand was guided by the performance of the dominant hand therefore reduced the attentional demand required for the bilateral finger tapping tasks. Further studies recruiting both left and right handers, as well as finding a means of manipulating the cognitive attentional demands by manipulating tasks complexity are warranted to clarify the results of studies utilizing DT paradigm.

Bilateral activation was evident in most studies investigating the cortical control of swallowing (Mosier et al., 1999a; Mosier et al., 1999b), however general agreement exists that activation of M1 is asymmetric (Hamdy et al., 1999b; Mosier et al., 1999a; Mosier et al., 1999b). It was previously reported that swallowing is bilaterally represented in the cortex with specialized role of each hemisphere, in that right hemisphere may mediate pharyngeal phase of swallowing and left hemisphere involved in the control of the voluntary oral phase of swallowing (Daniels et al., 2006). One could argue, however, that hemispheric specialization might be specific to different components of swallowing with some components equally represented in both hemispheres (Daniels et al., 2006). On this note, our data suggest that right M1 may be more actively involved in the initiation of pharyngeal swallowing, with the orchestration of pharyngeal muscles being bilaterally represented, as evidenced by a lack of effect of DT paradigm on pharyngeal pressure generation mechanisms. This assumption, however, is challenged by lack of effect of bilateral finger tapping task, which require bilateral cortical input, on the pharyngeal pressure generation, suggesting potential role of divided attention in the results of the current study.

In order to avoid the possible contribution of divided attention in the DT paradigm results and provide more focal neural disruption, single pulse TMS was

utilized to create neurophysiological disruption during the performance of swallowing and other motor behaviours along the neuraxis. The effect of TMS disruption to the submental muscles representation on M1from the dominant hemisphere on the regularity of swallowing provides further support of hemispheric dominance in the regulation of some aspects of pharyngeal swallowing. Our results confirm the findings of previous studies utilizing TMS to disrupt pharyngeal M1 (Jefferson et al., 2009; Mistry et al., 2007; Verin et al., 2012). It is speculated that the effect of TMS disruption on the regularity of swallowing was a result of alteration of the motor commands from M1 to the CPG in the brainstem. This assumption is supported by findings from animal studies in that lesions involving face M1 was found to alter but not prevent swallowing (Hiraba et al., 2007; Yamamura et al., 2002). The results of the current study provide further support to the findings of hemispheric lateralization in regulating pharyngeal swallowing reported in the study utilizing DT paradigm (chapter 6). While the DT paradigm study suggested possible involvement of the right M1 in the initiation of the pharyngeal swallowing act, the laterality of effect cannot be derived from the study utilizing TMS to disrupt M1 excitability as the laterality of hemispheric dominance varies across individuals. Given the assumption of M1 involvement in the initiation and timing of pharyngeal swallowing (Jefferson et al., 2009; Mistry et al., 2007; Verin et al., 2012), one would expect an effect on the rate of swallowing when M1 was disrupted using TMS. This was not evident in the current project. In contrast, utilizing behavioural disruption of the DT paradigm was found to alter both rate and regularity of swallowing. Methodological differences, in particular differences in the mean of neural disruption might explain the difference in results. The DT paradigm provided less focal disruption to M1 and the involvement of the other cortical areas such as SMA and premotor cortex could have contributed to the effect seen in the rate of swallowing. In addition, divided attention between the motor tasks could have exaggerated the effect of DT paradigm on the swallowing behaviour. Even though the effect of TMS disruption on the other cortical areas cannot be completely ruled out, one might argue that TMS produced the strongest disruption in the stimulated area providing cleaner means of investigating the M1 contribution in swallowing. TMS disruption was provided transiently in the current study, whereas continuous disruption was

delivered during the DT paradigm since tasks were performed concurrently for 7 sec. Therefore the transient disruption of TMS might not have been sufficient to disrupt the rate of swallowing. Findings from the current project may suggest that M1plays a role in regulating pharyngeal swallowing possibly through a balance of excitatory or inhibitory mechanisms to the CPG depending on the characteristics of the boluses (Mistry et al., 2007).

Interestingly, our data revealed similar effects of TMS stimulation to either hemisphere on the pharyngeal pressure generation. These findings suggest symmetrical hemispheric control to more complex components of pharyngeal swallowing, such as the pressure generation mechanisms. Creating electrophysiological disruption to M1 increased the duration of pharyngeal pressure generation in both swallowing types. The effect of TMS disruption on the duration of pharyngeal pressure could be due to the fact that single pulse TMS provides more focal disruption to M1 than DT paradigm. The duration of UES relaxation and the total duration of pharyngeal pressure generation were longer during the TMS disruption than before the disruption. This change in the duration of pharyngeal pressure could be a result of TMS modulation to the motor commands from M1 to the swallowing CPG. While TMS disruption affected the duration of pharyngeal pressure, it did not affect the amplitude of the pharyngeal pressure in the current study. Lack of effect of TMS disruption on the magnitude of pharyngeal muscle contraction could be due concomitant input from the non-disrupted hemisphere given that swallowing is bilaterally represented in the brain (Hamdy et al., 1999a; Hamdy et al., 1999b; Mosier et al., 1999a). The transient effect of single pulse TMS might have contributed to the lack of effect of TMS disruption on the amplitude of pharyngeal pressure. Utilizing single pulse TMS may have altered some aspects of the swallowing process due to transient nature of stimulation of this tool. Further studies utilizing longer lasting disruption mechanisms such as rTMS are warranted to verify this assumption.

Creating electrophysiological disruption on M1 was also found to affect the duration of pharyngeal pressure at the level of oropharynx in volitional but not reflexive swallowing. The duration of pressure at the upper pharyngeal sensor during

volitional swallowing was longer during TMS disruption than after the TMS disruption. This increase in pressure duration may be due to effects of TMS disruption on tongue movement. During volitional swallowing the tongue retracts to meet the posterior pharyngeal wall during the initiation of pharyngeal swallowing, therefore contacting the upper pharyngeal sensor. The TMS disruption of the motor commands from M1 might have caused longer base of tongue to posterior pharyngeal wall contact. These findings support the thought of larger involvement of M1 in the control of voluntary aspect of swallowing identified in previous research (Doeltgen et al., 2011; Huckabee et al., 2003; Jean, 2001; Jean & Dallaporta, 2006; Kern et al., 2001a; Martin et al., 2004).

In summary, the data of the present extended the understanding of the involvement of M1 in regulating pharyngeal swallowing. The data from this research programme suggest that M1 sends motor commands to the brainstem upon receiving the sensory information from the peripheral system. A disruption to the area of M1 has resulted in disruption of the regularity and the duration of the pressure generation extending the knowledge of the cortical control, in particular M1, of pharyngeal swallowing. Our data further support the hemispheric dominance of some components of swallowing such as the regularity of pharyngeal swallowing, with the more complex components such as pharyngeal contraction requiring more equally bilateral innervation.

9.3. **Limitations and future directions:**

A number of limitations have been identified in the current research programme. Shared cognitive attention between tasks could not be quantified in the study that investigated the effect of DT paradigm on swallowing and other motor behaviours. Future studies utilizing the same method should take this into account and develop methods to quantifying cognitive attention contribution to the results. Manipulating the complexity of the tasks might assist in quantifying the cognitive

attention by measuring the extent of the change in effect when the target behaviour is paired with more or less complex tasks.

Only right-handed individuals were recruited to this research programme; however, tasks recruiting both right and left hands were utilized. Given that the left hand was not the dominant hand, one might argue that utilizing the left hand required higher attention and mental resources. In fact, previous research identified contributions from both hemispheres during tasks performance with left hand in right-handed population (Callaert et al., 2011; Davare et al., 2007; Hortobágyi et al., 2003; Perez & Cohen, 2008; Swinnen & Wenderoth, 2004). Future studies should recruit both right and left-handed participants to eliminate the potential contribution of hand dominance in the results.

One might argue that the transient effect of unilateral single pulse TMS disruption was not sufficient to produce clear effects on the tightly bilateral controlled tasks such as jaw movement and swallowing when performed continually for a period of time. Future studies utilizing longer lasting disruption such that produced by rTMS, in addition to bilateral stimulation condition are warranted to clarify the current results and add to the knowledge of neural control of swallowing in particular.

The inclusion of a reflexive swallowing condition utilizing an automatic infusion pump in the current programme has added to the knowledge of neural control of different phases of swallowing. Even though contribution of oral structures, in particular tongue movement, was minimized during reflexive swallowing by bite-block and verbal instruction, oral contribution might not have been eliminated completely. In addition the current method of inducing reflexive swallowing was not well tolerated by some participants. This might have resulted in anticipation and voluntary preparation of bolus flow, such as tongue movement, despite the presence of bite-block over the tongue, and vocal adduction to protect the airway. These anticipatory behaviours might have provided voluntary components to the reflexive swallowing task. Measurement of swallowing-respiration coordination could have provided valuable information regarding the possible early vocal adduction in anticipation for the bolus during the reflexive swallowing task. Future

studies utilizing clearer methods to induce pharyngeal swallowing such as fluoroscopic guided naso-pharyngeal infusion of water to the pharynx might strengthen the method. However a number of limitation and risks should be considered, such as the risk of aspiration when delivering naso-pharyngeal continuous flow of water to the pharynx.

Discrete saliva and water swallowing was utilized extensively in previous research evaluating the neural control and biomechanics of swallowing. However, substantial biomechanical differences have been identified between the discrete and continuous swallowing (Chi-Fishman & Sonies, 2000; Daniels et al., 2004; Daniels & Foundas, 2001). Discrete swallowing was not utilized in the current studies investigating the contribution of M1 in the control of swallowing, posing a potential limitation in the current research programme. The large volume of water ingested in the current programme limited the ability to include further swallowing tasks to avoid bloating effect. Even though the contribution of M1 in the control of discrete swallowing could be inferred from previous studies utilizing this swallowing type (Jefferson et al., 2009; Mistry et al., 2007; Verin et al., 2012), a direct comparison between the previous results and the results of the current programme is limited as the former task was not included in the current studies and the methodologies are different. Future studies investigating the differences in the neural control between discrete and continuous swallowing are warranted given the clear biomechanical differences between these tasks.

A number of comparisons have been carried out during the statistical analysis of this research programme; therefore, Bonferroni correction was utilized to limit the effect of such a large number of comparisons. Bonferroni correction is applied to control for type I error when multiple comparisons are conducted (Nakagawa, 2004). An apparent limitation of applying Bonferroni correction is that it substantially reduces the statistical power of rejecting an incorrect null hypothesis in each test, therefore increasing the probability type II error (Nakagawa, 2004). Further, Bonferroni correction has been shown to be very conservative and it could potentially turn the previously significant results to non-significant.

The current study provided valuable information regarding the neural control of pharyngeal swallowing as inferred from the manometeric data. Manometry is a valuable tool that has been utilized frequently to quantify the pressure generation during swallowing. A number of limitations have been identified when using pharyngeal manometry. First, the sensors located within the manometric catheter are in a static position, therefore those sensors could be located at different locations across individuals given the anatomical differences of the pharynx across individuals. Second, the catheter is not stabilized in the pharynx allowing for the possibility of movement during the flow of the bolus in the pharynx. Third, measurement of intra-bolus pressure is not possible without combined visual guidance such as VFSS. Therefore, future studies should consider utilizing combined VFSS and manometry to further clarify the results of neural disruption on the biomechanics of swallowing and differentiate between the effects of intra-bolus pressure on pharyngeal pressure generation. In addition, combining VFSS with manometry would assess location of the sensors throughout the session. A potential difficulty would be the radiation exposure which may hinder the utilization of such techniques in lengthy recording sessions.

9.4. **Summary:**

This programme was the first to document the pharyngeal pressure differences between different swallowing types and has documented clear bio-mechanical differences between discrete and continuous swallowing as well as between saliva and water swallowing. The current programme extended the knowledge of the neural control of swallowing in that it is the first to document the role of M1 in the pharyngeal pressure generation. The current programme revealed novel contribution of M1 in the control of the regularity and the coordination of pharyngeal swallowing possibly by means of modulating the motor plan at the swallowing CPG in the brainstem.

The current programme also provided important methodological findings. This programme provided further insight to the feasibility of single pulse TMS to investigate causal-function relationship. Furthermore, the current research provided important methodological information regarding the DT paradigm in that utilizing quantifiable motor tasks that utilize similar neural pathways have shown clearer results than pairing two tasks that are not quantifiable or utilizing different neural pathways. In addition, finding a means of identifying the contribution of divided attention in the DT paradigm would strengthen the results from studies utilizing this method. Measuring the rate and regularity of task performance provides more in depth information about the task performance. The regularity of tasks was affected more than the rate in the current research project suggesting that measures of regularity different information than rate in detecting the effect of experimental disruption during the performance of motor tasks.

Chapter 10: **Concluding remarks:**

The results of this research programme expanded on previous knowledge of neural control of swallowing, in that they provided novel findings regarding the role of M1 in the pharyngeal pressure generation. To our knowledge, this research programme is the first to document the role of M1 in pharyngeal pressure generation during volitionally and reflexively initiated pharyngeal swallowing utilizing pharyngeal manometry. Our results revealed that the role of M1 in pharyngeal swallowing goes beyond the initiation and timing of pharyngeal swallowing and M1 plays a role in modulating the CPG plan for pharyngeal muscles coordination during swallowing. These findings were evidenced by observable reduction of the rate and regularity as well as increased duration of pharyngeal pressure when the area of M1 controlling pharyngeal swallowing was disrupted during the performance of swallowing tasks. It is hypothesised that the disruption to M1 resulted in disruption to the motor commands from M1 to the CPG in the brainstem. Studies manipulating the sensory input and recording changes in activation at the level of M1 and CPG in the brainstem are warranted to clarify these findings.

In addition, our findings confirmed the concept of hemispheric dominance of swallowing as providing electrophysiological disruption to the dominant hemisphere affected the regularity of pharyngeal swallowing. In addition, the current findings provided further support hemispheric lateralization of swallowing as pairing swallowing with left finger movement in the study utilizing the DT paradigm was found to yield an effect on the rate and regularity of swallowing. In contrast, creating electrophysiological disruption to the area of M1 controlling submental muscles from either hemisphere was found to affect the duration of pharyngeal pressure generation during swallowing. These findings suggests that hemispheric lateralization is likely be specific to some swallowing components, with certain components such as patterned pharyngeal musculature movement, being more bilaterally organized. Further studies utilizing longer lasting disruption mechanisms such as rTMS and providing simultaneous disruption to the M1 of both hemispheres are warranted to clarify these results. Understanding the neural control underlying healthy swallowing

system will facilitate understanding of disordered systems and could potentially guide development of appropriate rehabilitation techniques. Therefore, the current research has contributed to the understanding of the complex neural mechanisms underlying the swallowing system. Our findings provided further contribution regarding the involvement of M1 in the pharyngeal phase of swallowing.

To facilitate understanding of swallowing neural control, the current research also investigated the neural control of voluntary corticospinal and cortricobulbar tasks which are well documented in the literature. Our results provided further support to the active involvement of contralateral M1 in the execution of voluntary corticospinal tasks. Providing electrophysiological disruption to the contralateral hand M1 affected the rate and regularity of the finger tapping tasks. In addition, our findings supported the previous thought of bilateral M1 involvement in the control of voluntary corticobulbar tasks given that neural disruption to submental muscles representation on M1 from either hemisphere resulted in similar effects on the regularity of jaw movement task. The neural disruption to either hemisphere has altered the regularity of jaw movement but not the rate of the movement suggesting possible concomitant input from the non-disrupted hemisphere.

Furthermore, results from the current research provided insight into the functional neural organization of muscle representation within M1. Our results suggested that the neural substrates of corticospinal and corticobulbar tasks do not functionally overlap to a significant degree despite the possible topographical overlap between the representations of the hand and face muscles in M1. This assumption is supported by lack of effect of DT paradigm interference on finger tapping tasks when paired with eyebrow movement and swallowing tasks. In contrast, our results revealed potential bilateral functional overlapping to a significant degree between neural substrates that control swallowing and orofacial muscles as evident by the effect of swallowing on the rate and regularity of the eyebrow movement.

As a secondary aim of this research programme, the difference in pharyngeal pressure generation between four swallowing types was investigated utilizing pharyngeal manometry. This project was the first to document the pharyngeal

pressure differences between discrete and continuous swallowing providing novel contribution to the understanding of biomechanical differences between discrete and continuous swallowing. Our results revealed differences in pharyngeal pressure generation between swallowing types and boluses types. These differences should be taken into account when managing patients with swallowing difficulties. A study with combined VFSS and manometry is required to further clarify the results and identify the effect of intra-bolus pressure on the pharyngeal pressure generation measures.

In addition to expanding the knowledge of neural control of swallowing the current research provided methodological contributions. This research programme further supported the feasibility of single pulse TMS as neural disruption tool to investigate the contribution of cortical areas in behavioural functions. In addition, valuable methodological information were provided regarding the utilization of DT paradigm in swallowing in that pairing tasks that utilize similar neural pathways produces more apparent effects than pairing tasks utilizing different neural pathways. In addition, utilizing quantifiable tasks allow the evaluation of the effect of DT paradigm on both tasks providing more in-depth insight of the effect of the paradigm on the task performance. Finding a mean of quantifying the contribution of divided attention between tasks on the results of DT paradigm would strengthen the findings of the studies utilizing this paradigm and increase the reliability of this method to investigate neural organization of behavioural tasks. Measuring the rate and regularity of task performance provides more in depth knowledge than measuring either of them.

Part VI: References

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Appendices

APPENDIX I: EDINBURGH HANDEDNESS INVENTORY

Your Initials:_____

Please indicate with a check (✓) your preference in using your left or right hand in the following tasks.

Where the preference is so strong you would never use the other hand, unless absolutely forced to, put two checks (✓✓).

If you are indifferent, put one check in each column (✓ | ✓).

Some of the activities require both hands. In these cases, the part of the task or object for which hand preference is wanted is indicated in parentheses.

Task / Object	Left Hand	Right Hand
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (without fork)		
7. Spoon		
8. Broom (upper hand)		
9. Striking a Match (match)		
10. Opening a Box (lid)		
Total checks:	LH =	RH =
Cumulative Total	CT = LH + RH =	
Difference	D = RH – LH =	
Result	R = (D / CT) × 100 =	
Interpretation: (Left-handed: R < -40) (Ambidextrous: -40 ≤ R ≤ +40) (Right-handed: R > +40)		

APPENDIX II: INFORMATION SHEET. TMS DISRUPTION STUDY

Introduction and aims of the project:

You are invited to participate in a research project that evaluates how the brain controls different motor tasks in particular swallowing. The aim of this project is to evaluate the influence of disrupting the message sent from the brain to the muscles involved in a number of motor behaviours varying in complexity. Those motor behaviours will range from simple finger movement, to complex reflexive swallowing task. This disruption will be created using single pulse transcranial magnetic stimulation (TMS) applied over the area of the brain controlling the target muscle as explained in step (16).

Taking part in this study is voluntary (your choice) and you can withdraw from the study at any time. Any decision not to participate will not affect your current, continuing or future health care or academic progress. We would appreciate a decision regarding your participation within two weeks. This research is part of the principal investigator's PhD (Doctor of Philosophy) project.

Participant selection:

Your participation in this study is due to your reply to advertisements for research participants. Upon your consent, you will be selected for this study if you are aged 18 and above and have no medical problems that may affect your swallowing. The study will include a total of 24 right-handed participants of the same age group who have no swallowing problems and will require a session of approximately 3hrs duration.

Exclusion criteria:

You may not be eligible to participate in this study if you are left-handed or you have or ever have had any of the following conditions:

- seizure
- stroke
- metal in your head (outside the mouth) such as shrapnel, surgical clips, or fragments from welding or metalwork
- implanted devices such as cardiac pacemakers, medical pumps, or intracardiac lines
- frequent or severe headaches
- any brain-related condition or any illness that caused brain injury
- any cases of epilepsy in your family
- currently pregnant

Completing the Transcranial Magnetic Stimulation Adult Safety Screen, a handedness inventory and an additional brief questionnaire will ensure that inclusion criteria are met and risks are minimised.

The research procedure:

The research will take place at the Van der Veer Institute for Parkinson's and Brain Research. Below is a table showing the experimental tasks. Those tasks will be executed in randomised order.

Tasks:	Experimental conditions:	Outcome measures:
A) Rapid right index finger tapping. B) Rapid left index finger tapping.	Disruption of the tasks (A & B) with TMS.	- Changes in the number and regularity of finger tapping between baseline and during the disruption task as measured by finger tapping device.
C) Rapid up and down jaw movement.	Disruption of the task (C) with TMS.	- Changes in number and regularity of jaw movement between baseline and during the disruption task.
D) Rapid volitional swallowing of water through straw. E) Rapid reflexive swallowing of water by direct ingestion of water to the throat through a tube.	Disruption of the tasks (D & E) with TMS.	- Changes from baseline for the following measures: 1- MEPs difference between the first swallow and subsequent swallows. 2- Changes in Manometry wave and throat pressure. 3- Changes in number of swallows, total volume of water swallowed and volume of water swallowed per swallows.

If you agree to participate in the study, the following will occur:

1- You will be given an appointment and asked to come to the Swallowing Rehabilitation Research Laboratory at the Van der Veer Institute, 66 Stewart Street, Christchurch.
2- After signing the consent form, you will be asked to complete a standard safety questionnaire to screen for risk of adverse events during one of the procedures. Completing the Transcranial Magnetic Stimulation Adult Safety Screen will ensure that inclusion criteria are met and risks are

minimised. You will also be asked to fill in a brief questionnaire regarding your ethnic background and any medical conditions that may affect your swallowing.

3- You will then be seated in a comfortable chair and the researcher will ask you if you are ready to start. The following preparation procedures will be done:

For the finger tapping task:

4- You will be presented with a finger-tapping device. This device will be connected to a computer system. Each tap will complete an electrical circuit, which will be recorded and represented on the computer system.
5- A small pair of surface electrodes will be secured on the top of your arm muscles using a removable adhesive tape. You will be asked to rapidly tap your index finger for 7 seconds. As you do this, the electrodes will measure the amount of electrical activity you generate in your muscles during tapping. This will enable the researchers to adjust the equipment to your individual muscle activity during finger tapping task. This muscle activity will be used to trigger TMS in response to set threshold from the arm muscles for the experimental task.
6- You will be instructed to use your index finger when you are performing the task, and to keep your hand still by resting your hand and arms in a table placed in front of you.
7- You will perform the tasks rapidly for 7 seconds for each finger, right and left, without TMS disruption for baseline measurement, and then with the TMS disruption to identify the effect of brain signal disruption on the tasks.

***For rapid up and down jaw movement task*:**

8- A small pair of surface electrodes will be secured underneath your chin using a removable adhesive tape. You will be asked to rapidly move your jaw up and down for 7 seconds. As you do this, the electrodes will measure the amount of electrical activity you generate in your muscles during jaw movement. This will enable the researchers to adjust the equipment to your individual muscle activity during the performance of the experimental task. This muscle activity will be used to trigger TMS in response to set threshold from the chin muscles for the experimental task. After that you will be asked to execute the task in same manner as explained in step (7).

***For volitional and reflexive swallowing tasks*:**

9- Two types of swallowing will be tested in this study, "Volitional" and "Reflexive". The "Volitional swallowing task" requires you to drink water from a cup through a straw. In the "Reflexive swallowing task" water will be pushed directly into your throat through a tube. Volitional swallowing will include the water running through the mouth whereas the mouth will be bypassed in reflexive swallowing. This lets us evaluate if bypassing the mouth yields different results in how the brain controls swallowing.
10- A small microphone will be inserted in your ear canal to pick the swallowing acoustic signal to trigger the TMS for the swallowing tasks and this microphone will be sealed in the ear using foam eartip.
11- You will be asked to complete 10 water swallows to establish a threshold of the swallowing acoustic signal to trigger the TMS.
12- A small tube will be carefully inserted through one side of your nose. This tube is about the size of a piece of spaghetti and is very soft and flexible. As soon as the tube reaches the back of your throat, you will be required to look up to the ceiling briefly while the tube turns the corner into your upper throat. You will then be handed a glass of water and asked to continuously and comfortably drink the water through a straw. In doing so, the tube will be swallowed into the upper esophagus.
13- The tube will then be slowly pulled upwards until correct placement is assured in the throat. Once in the correct place, a small piece of first aid tape will be wrapped around the tube and secured on your nose to ensure the tube does not move while you swallow. Imbedded in the tube are three manometric pressure sensors that measure pressure in the throat.
14- You will be given few minutes to adjust to the feeling of the tube in the throat before commencing the experimental tasks.
15- For the volitional swallowing task, you will be asked to continuously drink water for 7 seconds from a cup through a straw.
16- For reflexive swallowing task, a tube will be inserted orally from the side of your mouth to elicit continuous reflexive swallowing. This tube will run through a small nylon holder to secure it in your mouth with the tip of the tube placed just behind your tongue. This will guide the water to flow into the space at the base of the tongue and ensure the safety of the airway. The rate and volume during the reflexive swallowing will be controlled and monitored using a pump controlled by the researcher. The water will run to your throat continuously for 7 seconds at each time. Upon the completion of the preparation for the task, you will then be asked to execute the tasks in similar manner as explained in step (7).

TMS stimulation:

17- The signal from your brain to the target muscles will be disrupted using a technique called transcranial magnetic stimulation (TMS). TMS consists of a figure-of-eight coil that is held over your scalp. When you activate the target muscles, the electrical activity in these muscles will trigger this coil to stimulate your brain using a magnetic pulse. This will feel like someone

is tapping you on the head but will not hurt. You may also feel a small twitch in the arm opposite the side of the brain being stimulated. When the magnetic pulse is triggered, your brain sends an electric signal to your muscles, which can then be measured using the electrodes placed under your chin, or on the top of your arm. This signal is called a motor evoked potential, or MEP.

18- For the assessment session we will need to identify which areas of the brain are activated by the magnetic stimulation and how to best apply that stimulation. Starting on the left side of your head, and then moving to the right, several steps need to be taken.
   i. First, the best area for stimulating brain signals (MEPs) will be identified by measuring the MEPs from several places on your scalp and finding which place gives the best response. The researcher will use TMS to find the place on your skull which creates the biggest signal. During this time you will feel a twitch in the muscles under your chin, or your hand muscles and a sensation of 'tapping' on your head. Once this area has been determined, the position of the coil will be marked on the scalp using a water soluble pen.
   ii. Next, we will evaluate how strong the magnetic pulse needs to be to stimulate your brain and what level is best for doing the research. Starting with a very soft 'tap', or magnetic pulse, we will slowly increase the intensity until we determine the lowest level of stimulation required is. Then we will increase the intensity until the signals do not get any larger.
   iii. These steps will be completed on both sides of your head. This will help the researchers identify the best area in both sides. All further MEP measurements will then be made at the identified locations on both sides of your head.

19- When you have finished these protocols, the equipment will be removed and you are free to go. The manometric tube data (throat pressure data) and the finger tapping data will be stored on the swallowing workstation, and the MEP data and the jaw movement data will be saved on the computer for subsequent analysis. No audio- or video-recordings of the testing session will be made. Confidentiality will be assured by assigning you a coded numerical identification and data will be stored in the locked Swallowing Rehabilitation Research Laboratory at the Van der Veer Institute.

Risks and Benefits:

There will be no direct benefit to you but you will be part of a study that contributes important information regarding how the brain controls motor behaviours and swallowing.

There are no documented complications of insertion of the small manomentry tube through the nose. Single pulse TMS which is applied in this study, is thought to carry little risk beyond occasionally causing local discomfort at the site of stimulation and headaches that last for a short while in participants who are prone to headache. There are conditions that may increase the risk for adverse effects of TMS (e.g., History of: seizures, head injury, stroke). Screening you with the Transcranial Magnetic Stimulation Adult Safety Screen will identify if you are at risk before you agree to participate.

You will be monitored very carefully by the researchers for any negative outcomes arising from your participation in this study. Facilities for emergency medical management, including suctioning and intubation, are available in the Swallowing Research Laboratory where the experiment is completed. Further medical help will be available from the patient care wards and the Emergency Cardiac Response team at hospital should any complications arise.

Compensation:

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention, Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigator. If you have questions about ACC, contact your nearest ACC officer or the investigator.

Participation:

If you do agree to take part in this study, you are free to withdraw at any time, without having to give a reason. This will in no way affect any future care or treatment. Your participation in the study will be stopped should any harmful effects appear or if you feel it is not in your best interest to continue.

Confidentiality:

Research findings will be presented at International Research Meetings and will be submitted for publication in relevant peer-reviewed journals. Additionally, research findings will be made available to the local Canterbury Medical Community through research presentation and regional forums. However, no material which could personally identify you will be used in any reports on this study. Consent forms will

be kept in a locked filing cabinet in the locked swallowing research laboratory or will be stored on password-protected laboratory computers. Research data will be stored for a period of 10 years after data collection is completed, at which time they will be destroyed.

With your permission, data from this study may be used in future related studies, which have been given ethical approval from a Health & Disability Ethics Committee.

Results:

You will be offered copies of the final manuscript of this project or a summary in lay language. However, you should be aware that a significant delay may occur between completion of data collection and the final report. Alternatively, or in addition, you can choose to have the results of the study discussed with you personally by the principal investigator.

Questions:

You can contact the principal investigator if you require any further information about the study. The principal investigator, **Aamir Al-Toubi**, can be contacted during work hours at **(03) 378 6348** or via email: **akt35@uclive.ac.nz**

If you need an interpreter, this can and will be provided.

This study has been given approval by the Upper South A Regional Ethics Committee.

If you have any questions or concerns about your rights as a participant in this research study, you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act.

Telephone (NZ wide): 0800 555 050. Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT)

Email (NZ wide): advocacy@hdc.org.nz

APPENDIX III: INFORMATION SHEET. DUAL-TASK STUDY

Introduction and aims of the project:

You are invited to participate in a research project that evaluates how the brain controls swallowing. The aim of this project is to investigate how the brain controls pharyngeal swallowing using a procedure which pairs swallowing with another motor task (finger tapping) that uses the primary motor cortex in the brain. If swallowing uses the same brain region, the tasks should be performed more poorly when performed together. A secondary aim of the study will be to identify the differences in pressure in the throat between different types of swallowing (single water swallowing, volitional continuous swallowing, and reflexive continuous swallowing). These pressures are part of the determining factors of a successful swallow.

Taking part in this study is voluntary (your choice) and you can withdraw from the study at any time. Any decision not to participate will not affect your current, continuing or future health care or academic progress. We would appreciate a decision regarding your participation within two weeks. This research is part of the principal investigator's PhD (Doctor of Philosophy) project.

Participant selection:

Your participation in this study is due to your reply to advertisements for research participants. Upon your consent, you will be selected for this study if you are aged 18 and above and have no medical problems that may affect your swallowing. The study will include a total of 24 right-handed participants of the same age group who have no swallowing problems and will require a session of approximately 3hrs duration.

The research procedure:

The research will take place at the Van der Veer Institute for Parkinson's and Brain Research. Below is a table showing the experimental tasks. Those tasks will be executed in randomised order.

Discrete VS continuous swallowing conditions:	Baseline swallowing and finger tapping conditions:	experimental tasks for swallowing and finger tapping conditions:
1) Ten saliva swallows at rate of one swallow every 30 seconds. 2) Ten discrete water swallows at rate of one swallow every 30 seconds. 3) Volitional continuous water swallowing for 7 seconds. 4) Reflexive continuous water swallowing for 7 seconds.	1)Finger tapping with the right index finger as rapidly as possible for 7 seconds. 2)Finger tapping with the left index finger as rapidly as possible for 7 seconds. 3)Finger tapping with both index fingers as rapidly as possible for 7 seconds. 4)Eyebrow movement as rapidly as possible for 7 seconds. 5)Rapid volitional swallowing of water for 7 seconds. 6)Rapid reflexive swallowing of water for 7 seconds.	7)Finger tapping with the right index finger as rapidly as possible during: (a) Rapid volitional water swallowing. (b) Rapid reflexive water swallowing. (c) Rapid eyebrow movement. 8)Finger tapping with the left index finger as rapidly as possible during: (a) Rapid volitional water swallowing. (b) Rapid reflexive water swallowing. (c) Rapid eyebrow movement. 9)Finger tapping with both index fingers as rapidly during: (a) Rapid volitional water swallowing. (b) Rapid reflexive water swallowing. (c) Rapid eye brow movement. 10) Eyebrow movement as rapidly as possible during: (a) Rapid volitional water swallowing. (b) Rapid reflexive water swallowing.

If you agree to participate in the study, the following will occur:

20- You will be given an appointment and asked to come to the Swallowing Rehabilitation Research Laboratory at the Van der Veer Institute, 66 Stewart Street, Christchurch.
21- You will then be seated in a comfortable chair and the researcher will ask you if you are ready to start. The following preparation procedures will be done:

22- A small tube will be carefully inserted through one side of your nose. This tube is about the size of a piece of spaghetti and is very soft and flexible. As soon as the tube reaches the back of your throat, you will be required to look up to the ceiling briefly while the tube turns the corner into your upper throat. You will then be handed a glass of water and asked to continuously and comfortably drink the water through a straw. In doing so, the tube will be swallowed into the upper esophagus.
23- The tube will then be slowly pulled upwards until correct placement is assured in the throat. Once in the correct place, a small piece of first aid tape will be wrapped around the tube and secured on your nose to ensure the tube does not move while you swallow. Imbedded in the tube are three manometric pressure sensors that measure pressure in the throat.
24- You will be given few minutes to adjust to the feeling of the tube in the throat before commencing the experimental tasks.

For the finger tapping task:

25- You will be presented with a finger-tapping device. This device will be connected to a computer system. Each tap will complete an electrical circuit, which will be recorded and represented on the computer system.
26- You will be instructed to use your index finger when you are performing the task, and to keep your hand still by resting your hand and arms on a table placed in front of you.
27- You will perform the tasks rapidly for 7 seconds for each finger, right and left, for baseline measurement, and then with volitional and reflexive continuous water swallowing, and with eyebrow movement to identify the effect of performing two tasks concurrently on each other.

For the eyebrow movement task:

28- A small pair of surface electrodes will be secured to the skin surface overlying your eyebrow using a removable adhesive tape.
29- You will perform the tasks rapidly for 7 seconds for baseline measurement, and then with volitional and reflexive continuous water swallowing to identify the effect of performing two tasks concurrently on each other.

***For volitional and reflexive swallowing tasks*:**

30- Two types of swallowing will be tested in this study, “Volitional” and “Reflexive”. The “Volitional swallowing task” requires you to drink water from a cup through a straw. In the “Reflexive swallowing task” water will be pushed directly into your throat through a tube. Volitional swallowing will include the water running through the mouth whereas the mouth will be bypassed in reflexive swallowing. This lets us evaluate if bypassing the mouth yields different results in how the brain controls swallowing.

31- For the volitional swallowing task, you will be asked to continuously drink water for 7 seconds from a cup through a straw.
32- For reflexive swallowing task, a tube will be inserted orally from the side of your mouth to elicit continuous reflexive swallowing. This tube will run through a small nylon holder to secure it in your mouth with the tip of the tube placed just behind your tongue. This will guide the water to flow into the space at the base of the tongue and ensure the safety of the airway. The rate and volume during the reflexive swallowing will be controlled and monitored using a pump controlled by the researcher. The water will run to your throat continuously for 7 seconds at each time.
33- Upon the completion of the preparation for the task, you will then be asked to execute the tasks listed in the table above in random order following the researcher's instructions.
34- When you have finished these protocols, the equipment will be removed and you are free to go. The throat pressure data, the finger tapping data and the eyebrow movement data will be stored on computer for subsequent analysis. No audio- or video-recordings of the testing session will be made. Confidentiality will be assured by assigning you a coded numerical identification and data will be stored in the locked Swallowing Rehabilitation Research Laboratory at the Van der Veer Institute.

Risks and Benefits:

There will be no direct benefit to you but you will be part of a study that contributes important information regarding how the brain controls motor behaviours and swallowing.

There are no documented complications of insertion of the small manomentry tube through the nose. You will be monitored very carefully by the researchers for any negative outcomes arising from your participation in this study. Facilities for emergency medical management, including suctioning and intubation, are available in the Swallowing Research Laboratory where the experiment is completed. Further medical help will be available from the patient care wards and the Emergency Cardiac Response team at hospital should any complications arise.

Compensation:

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention, Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation

payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigator. If you have questions about ACC, contact your nearest ACC officer or the investigator.

Participation:

If you do agree to take part in this study, you are free to withdraw at any time, without having to give a reason. This will in no way affect any future care or treatment. Your participation in the study will be stopped should any harmful effects appear or if you feel it is not in your best interest to continue.

Confidentiality:

Research findings will be presented at International Research Meetings and will be submitted for publication in relevant peer-reviewed journals. Additionally, research findings will be made available to the local Canterbury Medical Community through research presentation and regional forums. However, no material which could personally identify you will be used in any reports on this study. Consent forms will be kept in a locked filing cabinet in the locked swallowing research laboratory or will be stored on password-protected laboratory computers. Research data will be stored for a period of 10 years after data collection is completed, at which time they will be destroyed.

With your permission, data from this study may be used in future related studies, which have been given ethical approval from a Health & Disability Ethics Committee.

Results:

You will be offered copies of the final manuscript of this project or a summary in lay language. However, you should be aware that a significant delay may occur between completion of data collection and the final report. Alternatively, or in addition, you can choose to have the results of the study discussed with you personally by the principal investigator.

Questions:

You can contact the principal investigator if you require any further information about the study. The principal investigator, **Aamir Al-Toubi**, can be contacted during work hours at **(03) 378 6348** or via email: **akt35@uclive.ac.nz**

If you need an interpreter, this can and will be provided.

This study has been given approval by the Upper South A Regional Ethics Committee.

If you have any questions or concerns about your rights as a participant in this research study, you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act.

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Email (NZ wide): advocacy@hdc.org.nz

APPENDIX IV: HEALTH QUESTIONNAIRE

QUESTIONNAIRE

The role of primary motor cortex (M1) in pharyngeal swallowing.

Identifying number:_____ Age:_____

Which ethnic group do you belong to:

- ☐ New Zealand European
- ☐ New Zealand Maori
- ☐ Samoan
- ☐ Cook Island Maori
- ☐ Tongan
- ☐ Niuean
- ☐ Chinese
- ☐ Indian
- ☐ Other _____

Please complete the following questionnaire by ticking the box that is most applicable to you.

- do you suffer from the effects of any of the following medical problems?

- ☐ Stroke
- ☐ Swallowing difficulties
- ☐ Head and/or neck injury
- ☐ Head/ and/or neck surgery
- ☐ Neurological disorders (eg. Multiple Sclerosis etc.)
- ☐ Gastroesophageal Reflux Disease

Are you currently taking any medications that may affect your swallowing?

Yes / No (Please circle one)

If yes, please describe

_____

- do you suffer from the effects of any of the following medical problems?

- ☐ Family history of epilepsy
- ☐ History of seizures
- ☐ Muscular disease (e.g., Muscular atrophy)
- ☐ Any metal in your body (e.g., pacemaker, metal implants in the head or neck)
- ☐ Do you have any other medical problems which you feel may impact on your ability to participate (eg, inability to understand instructions)?

Yes / No (Please circle one)

If yes, please describe *(use reverse if necessary)*

APPENDIX V: CONSENT FORM

CONSENT FORM

The role of the primary motor cortex (M1) in pharyngeal swallowing.

English	I wish to have an interpreter.	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero.	Ae	Kao
Samoan	Oute mana'o ia iai se fa'amatala upu.	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea.	Io	Ikai
Cook Island	Ka inangaro au i tetai tangata uri reo.	Ae	Kare
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu.	E	Nakai

I have read and I understand the Information Sheet for volunteers taking part in the study designed to evaluate the role of the motor cortex in pharyngeal swallowing. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.

I have had the opportunity to use whanau support or a friend to help me ask questions and understand the study

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time. I understand that if I choose to withdraw from the study, I may also withdraw all information that I have provided.

I understand that the information obtained from this research may be published. However, I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study.

I understand that the investigation will be stopped if it should appear harmful to me and I know whom to contact if I have any side effects to the study or have any questions about the study.

I understand there are potential risks of participation in the study as explained to me by the researcher, and I have filled out the TASS questionnaire and the generic questionnaire, and I understand these minimise the risks of my participation.

I consent to the use of my data for future related studies, which have been given ethical approval from a Health and Disability Ethics Committee.

I have had time to consider whether to take part.

I wish to receive a copy of the results.
YES / NO
* Please note that a significant delay may occur between data collection and publication of the results

I would like the researcher to discuss the outcomes of the study with me
YES / NO

I, _____ hereby consent to take part in this study.

Signature_____Date_____
Signature of researcher: _____

Name of primary researcher and contact phone numbers:
Aamir Al-Toubi
Work ph. 03 378-6348
Mobile ph. 0210769609

(Note: A copy of the consent form to be retained by participant)

APPENDIX VI: TMS SAFETY QUESTIONNAIRE

Transcranial Magnetic Stimulation† (TMS) Adult Safety Screen

Name: Age: Date:

Please answer the following:

Have you ever:

Had an adverse reaction to TMS? □Yes □No

Had a seizure? □Yes □No

Had an electroencephalogram (EEG)? □Yes □No

Had a stroke? □Yes □No

Had a serious head injury (include neurosurgery)? □Yes □No

Do you have any metal in your head (outside the mouth) such as shrapnel, surgical clips, or fragments from welding or metalwork? □Yes □No

Do you have any implanted devices such as cardiac pacemakers, medical pumps, or intracardiac lines? □Yes □No

Do you suffer from frequent or severe headaches? □Yes □No

Have you ever had any other brain-related condition? □Yes □No

Have you ever had any illness that caused brain injury? □Yes □No

Are you taking any medications? □Yes □No

If you are a woman of childbearing age, are you sexually active, and if so, are you *not using* a reliable method of birth control? □Yes □No

Does anyone in your family have epilepsy? □Yes □No

Do you need further explanation of TMS and its associated risks? □Yes □No

*If you answered **yes** to any of the above, please provide details (use reverse if necessary):*

_____
_

† *For use with single-pulse TMS, paired-pulse TMS, or repetitive TMS.*

APPENDIX VII: PARTICIPANTS ADVERTISEMENT

The University of Canterbury Swallowing Rehabilitation Research Laboratory is looking for participants for a study to investigate

The role of the primary motor cortex in volitional and reflexive pharyngeal swallowing.

We are looking for healthy right-handed men and women

aged 18 years and above

This study will take place at the Van Der Veer Institute

for Parkinson's and Brain Research

66 Stewart Street, Christchurch, NZ

This project consists of two studies.
Each study will take approximately 3 hrs of your time.

You will be reimbursed for your travel expenses to and from the institute.

If you are interested and would like more information, please contact

Aamir Al-Toubi

Van der Veer Institute, 66 Stewart St. Christchurch NZ

Ph: 03 3786348 or 0210769609 or Email: akt35@uclive.ac.nz