

The Effects of Neuromuscular Electrical Stimulation of the
Submental Muscle Group on the Excitability of Corticobulbar
Projections

A Thesis Submitted in Partial Fulfilment of the

Requirements for the Degree

of Doctor of Philosophy

Sebastian H. Doeltgen

Department of Communication Disorders,

The University of Canterbury, Christchurch, New Zealand

29th April 2009

Keywords: Neuromuscular electrical stimulation (NMES), transcranial magnetic stimulation (TMS), motor evoked potential (MEP), deglutition, motor control

Acknowledgements

The completion of this thesis, and the preceding years of research and study, have been an inspiring source of academic and personal growth. Many people have supported me in the course of this adventure, and without their help, this thesis would not have been completed.

First and foremost, I would like to express my sincere gratitude to Dr Maggie-Lee Huckabee for her enthusiastic supervision, important advice and constant encouragement. She has inspired me to never cease to seek knowledge and understanding, and has shown me that research can, besides all challenges, be a lot of fun. Her trust and friendship have been a great source of motivation. I would also like to gratefully acknowledge my secondary supervisor, Associate Professor John Dalrymple-Alford, who has made many valuable suggestions and has given constructive advice throughout my studies.

I wish to express my cordial appreciation to our collaborators Mr Richard Dove and his engineering team at the Department of Medical Physics and Bioengineering, Canterbury District Health Board, Christchurch, New Zealand for their continued and invaluable support in all technical aspects of this research programme. The data analysis software designed by Dr Greg O'Beirne has been of great value in the data analysis process and is hugely appreciated. I would also like to thank Associate Professor Michael Ridding for sharing his extensive expertise in MEP research and his valuable help in the methodological design of this research programme.

My fellow researchers at the Van der Veer Institute for Parkinson's and Brain Research, Christchurch, New Zealand have always supported me through a continued exchange of ideas and much appreciated brainstorming sessions, which have helped me develop new skills and research questions. I am also grateful to my fellow postgraduate students at the Swallowing Rehabilitation Research Lab, who over the years have become good friends and strong support people. I would like to acknowledge Lipyn Leow, Janina Willmskoetter and Phoebe Macrae for their invaluable advice and help at various stages throughout my studies, in particular

with data analysis and interpretation, and a countless number of trial runs. I am privileged to have been able to learn from and work with them.

This research could not have been completed without the generous help of all the research participants who have volunteered many hours of their time. I appreciate their patience and perseverance, especially when research sessions were lengthy and uncomfortable, and their noble commitment to this research.

I would like to thank my family for their continuing encouragement and never ending love and friendship. I am forever indebted to my parents who have so generously supported me throughout my years of study, and whose motivating and reassuring words, and love have accompanied me along the way. Without their unreserved support of my plans and decisions, my studies would have been substantially more challenging and difficult. I am also grateful for the support of my friends in New Zealand and overseas. Beth and the late Cliff Marsden have been very special support people and their friendship means a lot to me.

My final, and most heartfelt thanks goes to my wife Rebecca, whose unconditional love and support have been a source of comfort, and motivation for long hours in front of the computer or weekends of data collection in the lab. She has helped me concentrate on completing this dissertation and has been a patient and helping hand in the proof reading stages of this thesis. Above all, she has given me the greatest gift of all: our beautiful daughter Zara Alice, born just a few days before the due date of this thesis, whose happy little personality makes everything else seem trivial.

TABLE OF CONTENTS

Acknowledgements	2
Abbreviations and Definitions	10
Abstract	11
Preface	13
 PART I	
Chapter 1 Introduction	16
Chapter 2 Swallowing Neurophysiology	20
2.1 <i>Cortical Control of Swallowing</i>	23
2.2 <i>Summary, Limitations and Future Directions</i>	34
Chapter 3 Electrical Stimulation in Rehabilitation	38
3.1 <i>Basic Principles of Neuromuscular Physiology</i>	38
3.2 <i>Basic Principles of Neuromuscular Electrical Stimulation</i>	41
3.3 <i>Sensory Versus Motor Stimulation</i>	47
3.4 <i>Application of NMES in Physical Rehabilitation Medicine</i>	50
3.4.1 <i>Effects of NMES on biomechanical function and peripheral motor recovery</i>	50
3.4.2 <i>Effects of NMES on cortical mechanisms</i>	59
3.4.3 <i>Early hypotheses regarding NMES-induced changes in CNS function</i>	61
3.5 <i>Review of Existing Research into the Effects of NMES on Swallowing Function and Neurophysiology</i>	63
3.5.1 <i>Effect of NMES on clinical swallowing function and swallowing biomechanics</i>	64
3.5.2 <i>Emergence of a new modality: VitalStimTM</i>	69
3.5.3 <i>Effects of NMES on swallowing related neurophysiological data</i>	77
3.5.4 <i>Literature reviews on the role of NMES in swallowing rehabilitation</i>	82
3.6 <i>Terminology</i>	83
3.7 <i>Risks and Contraindications</i>	84
3.8 <i>Summary</i>	86
Chapter 4 Transcranial Stimulation of the Human Brain	88
4.1 <i>Historical Development</i>	88
4.1.1 <i>Electrical brain stimulation</i>	88
4.1.2 <i>Magnetic brain stimulation</i>	89

4.2	<i>Physical Principles and Technical Characteristics</i>	91
4.3	<i>Components and Technical Design</i>	93
4.3.1	<i>Induction of current in neural tissue</i>	94
4.4	<i>Motor Evoked Potentials</i>	100
4.4.1	<i>Facilitation of MEP parameters</i>	103
4.4.2	<i>Variability of MEP parameters</i>	106
4.4.3	<i>Effect of training on MEP amplitude</i>	108
4.5	<i>Motor Evoked Potentials in Corticobulbar Muscles</i>	109
	Statement of Current Questions	117
	Chapter 5 Hypotheses	120
PART II		
	Chapter 6 Methodology	132
6.1	<i>Ethical Approval</i>	132
6.2	<i>Materials</i>	132
6.2.1	<i>Muscles under investigation</i>	133
6.2.2	<i>Submental surface electromyography and recording system</i>	133
6.2.3	<i>Custom-built trigger system</i>	136
6.2.4	<i>Electrical stimulator</i>	136
6.2.5	<i>Magnetic stimulator</i>	137
6.2.6	<i>Analysis software</i>	138
6.2.7	<i>Definition of neuromuscular electrical stimulation</i>	139
6.3	<i>Pre treatment Procedures</i>	141
6.3.1	<i>Participants</i>	141
6.3.2	<i>Electrode placement</i>	141
6.3.3	<i>Practice of research tasks</i>	143
6.3.4	<i>Trigger threshold</i>	144
6.3.5	<i>Identification of optimal scalp location</i>	144
6.3.6	<i>Electrical stimulus intensity</i>	145
6.4	<i>Data Collection Procedures</i>	146
6.5	<i>Data Processing and Analysis</i>	147
PART III		
	Chapter 7 Evaluation of MEP Reliability Measures	148
7.1	<i>Methods Inter- and Intra-session Reliability</i>	149
7.1.1	<i>Participants</i>	149
7.1.2	<i>Data recording</i>	150
7.1.3	<i>Data preparation and analysis</i>	150
7.2	<i>Results Inter- and Intra-session Reliability</i>	152
7.2.1	<i>Intra-session reliability – MEP amplitude</i>	152
7.2.2	<i>Intra-session reliability – MEP onset latency</i>	152
7.2.3	<i>Inter-session reliability – MEP amplitude</i>	155
7.2.4	<i>Inter-session reliability – MEP onset latency</i>	157
7.3	<i>Results Inter- and Intra-rater Reliability</i>	158

7.3.1	<i>Inter-rater reliability</i>	158
7.3.2	<i>Intra-rater reliability</i>	158
7.4	Discussion	160
7.4.1	<i>Inter- and intra-session reliability</i>	160
7.4.2	<i>Inter- and intra-rater reliability</i>	161
7.5	Conclusions	162

Chapter 8 The Effects of Repeated Volitional Swallowing and Time on MEP Amplitude and Onset Latency 163

8.1	Methods	165
8.1.1	<i>Participants</i>	165
8.1.2	<i>Data recording and experimental protocols</i>	165
8.1.3	<i>Data analysis</i>	166
8.2	Results	166
8.2.1	<i>Amplitude</i>	166
8.2.2	<i>Onset latency</i>	167
8.3	Discussion	168

PART IV

Chapter 9 Task-Dependent Differences in the Excitability of Corticobulbar Projections to the Submental Musculature: Implications for Neural Control of Swallowing 172

9.1	Methods	175
9.1.1	<i>Participants</i>	175
9.1.2	<i>Data acquisition</i>	176
9.1.3	<i>Transcranial magnetic stimulation of submental motor cortex</i>	177
9.1.4	<i>Muscle contraction conditions</i>	178
9.2	Results	179
9.2.1	<i>MEPs recorded during VC versus MEPs recorded during VPS</i>	179
9.2.2	<i>MEP amplitude</i>	180
9.2.3	<i>MEP onset latency</i>	180
9.3	Discussion	182
9.4	Conclusions	188

PART V

Chapter 10 Effects of Stimulus Frequency on the Excitability of Submental Corticobulbar Projections..... 189

10.1	Methods	191
10.1.1	<i>Participants</i>	191
10.1.2	<i>Pre treatment preparation and baseline recording</i>	192
10.1.3	<i>Research protocols</i>	193
10.1.4	<i>Post treatment outcome measurement</i>	193
10.1.5	<i>Data preparation and analysis</i>	194
10.2	Results	194

10.2.1	<i>MEP amplitude</i>	194
10.2.2	<i>MEP onset latency</i>	195
10.3	Discussion	198
10.4	Conclusions	203
Chapter 11	Effect of Treatment Dose on the Excitability of Submental Corticobulbar Projections	205
11.1	Methods	206
11.1.1	<i>Participants</i>	206
11.1.2	<i>Data recording and NMES treatment</i>	206
11.1.3	<i>Data preparation and analysis</i>	207
11.2	Results	208
11.2.1	<i>Effect of dose on MEP amplitude</i>	208
11.2.2	<i>Effect of dose on MEP onset latency</i>	209
11.3	Discussion	211
11.4	Conclusions	212
 PART VI		
Chapter 12	Replication of Treatment Effects After 80 Hz NMES	213
12.1	Methods	214
12.1.1	<i>Participants</i>	214
12.1.2	<i>Research protocol</i>	214
12.1.3	<i>Data preparation and analysis</i>	215
12.2	Results	215
12.2.1	<i>MEP amplitude</i>	215
12.2.2	<i>MEP onset latency</i>	216
12.3	Discussion	217
12.4	Conclusions	218
Chapter 13	Comparison of the Effects of Event-related and Non-event-related NMES	219
13.1	Methods	221
13.1.1	<i>Participants</i>	221
13.1.2	<i>Data acquisition</i>	221
13.1.3	<i>Non-event-related NMES</i>	221
13.1.4	<i>Continuous NMES</i>	222
13.1.5	<i>Data preparation and analysis</i>	222
13.2	Results	223
13.2.1	<i>Event-related versus non-event-related NMES – MEP amplitude</i>	223
13.2.2	<i>Non-event-related NMES versus 1 hr continuous NMES – MEP amplitude</i>	224
13.2.3	<i>Effect of treatment protocols 8 and 9 on MEP onset latency</i>	226
13.3	Discussion	228
13.4	Conclusions	230

PART VII

Chapter 14 Discussion	232
14.1 Methodological Considerations	233
14.2 Implications for the Neural Control of Swallowing	238
14.3 NMES Treatment Parameters and the Role of NMES in Swallowing Rehabilitation	243
14.4 Limitations, Relevance and Future Directions	250
Chapter 15 Concluding Remarks	254
References	256
Appendices	278
Appendix 1 Electrical Stimulator Manual	278
Appendix 2 Research Advertisement	280
Appendix 3 Transcranial Magnetic Stimulation Adult Safety Screen	281
Appendix 4 Edinburgh Handedness Questionnaire	282
Appendix 5 Health Questionnaire	283
Appendix 6 Statistical Data Trial Effects Volitional Contraction	284
Appendix 7 Statistical Data Trial Effects Volitional Pharyngeal Swallowing	285
Appendix 8 Changes in MEP Onset Latency Volitional Contraction	286
Appendix 9 Changes in MEP Onset Latency Volitional Pharyngeal Swallowing	287

LIST OF FIGURES

Figure 1	Electric current spread	42
Figure 2	Nerve fibre depolarisation	44
Figure 3	Muscle contraction and NMES frequency	45
Figure 4	Silvanus Thompson	90
Figure 5	Induction of electric current into the brain	93
Figure 6	Schematic diagram of a magnetic stimulator	94
Figure 7	Time course of magnetic field induction	95
Figure 8	Electric current and nerve fibre orientation	96
Figure 9	Round stimulation coil	99
Figure 10	Figure-of-8 stimulation coil	100
Figure 11	TMS intensity and MEP amplitude	102
Figure 12	Variability of MEP amplitude	108
Figure 13	Overview of research programme	131
Figure 14	Anterior hyo-mandibular musculature	134
Figure 15	Data acquisition system	135
Figure 16	Trigger system and electrical stimulator	137
Figure 17	Magnetic stimulator	138

Figure 18	Data analysis software	140
Figure 19	Surface electrode placement	143
Figure 20	Representative MEP waveforms: reliability analysis	153
Figure 21	Representative MEP waveforms of various muscle contraction conditions.....	181
Figure 22	Pyramidal cortical control model.....	184
Figure 23	Non-pyramidal cortical modulation model.....	186
Figure 24	Effect of frequency on MEP amplitude during volitional contraction	196
Figure 25	Effect of frequency on MEP amplitude during pharyngeal swallowing .	197
Figure 26	Effect of dose on MEP amplitude	210
Figure 27	Replication of 80 Hz NMES treatment trial	217
Figure 28	Effect of task context on MEP amplitude.....	225

LIST OF TABLES

Table 1	Differences in MEP amplitude across blocks and recording sessions.....	155
Table 2	MEP amplitude: reliability analysis.....	156
Table 3	Inter-session reliability of MEP amplitude: intraclass correlation coefficients.....	156
Table 4	MEP onset latency: reliability analysis.....	157
Table 5	Inter-session reliability of MEP onset latency: intraclass correlation coefficients	158
Table 6	Inter-rater reliability: MEP amplitude and onset latency	159
Table 7	Intra-rater reliability: MEP amplitude and onset latency	159
Table 8	Effect of swallowing and rest: mean MEP amplitudes.....	167
Table 9	Effect of swallowing and rest: mean MEP onset latencies.....	168
Table 10	Effect of NMES dose: mean MEP amplitudes	227
Table 11	Effect of NMES dose: mean MEP onset latencies	228

Abbreviations and Definitions

ALS	Amyotrophic lateral sclerosis
ANOVA	Analysis of variance
BOT	Base of tongue
BP	Bereitschaftspotential (or: readiness potential)
CPG	Central pattern generator
CMCT	Central motor conduction time
EEG	Electroencephalography
Event-related	NMES triggered from submental sEMG associated with the pharyngeal phase of a volitionally initiated swallow
FEES	Fibre-endoscopic evaluation of swallowing
fMRI	Functional magnetic resonance imaging
IPAS	Interventional paired associative stimulation
LTP	Longterm potentiation
LTD	Longterm depression
M1	Primary motor cortex
MEG	Magnetoencephalography
MEP	Motor evoked potential
NA	Nucleus ambiguus
NMES	Neuromuscular electrical stimulation
Non-event-related	NMES triggered automatically while musculature relaxed
NTS	Nucleus tractus solitaries
PET	Positron emission tomography
RPS	Reflexively initiated pharyngeal swallow
SD	Standard deviation
sEMG	Surface electromyography
SLN	Superior laryngeal nerve
SMA	Supplementary motor area
Submental	Anterior hyo-mandibular muscle group, consisting of the mylohyoid, geniohyoid and digastric (anterior belly) muscles
TMS	Transcranial magnetic stimulation
UOS	Upper oesophageal sphincter
VC	Volitional contraction condition
VFSS	Videofluoroscopic swallowing study
VPS	Volitionally initiated pharyngeal swallow

ABSTRACT

Neuromuscular electrical stimulation (NMES) has become an increasingly popular rehabilitative treatment approach for swallowing disorders (dysphagia). However, its precise effects on swallowing biomechanics and measures of swallowing neurophysiology are unclear. Clearly defined NMES treatment protocols that have been corroborated by thorough empirical research are lacking. The primary objective of this research programme was therefore to establish optimal NMES treatment parameters for the anterior hyo-mandibular (submental) musculature, a muscle group that is critically involved in the oral and pharyngeal phases of swallowing. Based on previous research, the primary hypothesis was that various NMES treatment protocols would have differential effects of either enhancing or inhibiting the excitability of corticobulbar projections to this muscle group. The research paradigm used to test this hypothesis was an evaluation of MEP amplitude and onset latency, recorded in the functional context of volitional contraction of the submental musculature (VC) and contraction of this muscle group during the pharyngeal phase of volitional swallowing (VPS, volitional pharyngeal swallow). Outcome measures were recorded before and at several time points after each NMES treatment trial. This methodology is similar to, but improved upon, research paradigms previously reported.

Changes in corticobulbar excitability in response to various NMES treatment protocols were recorded in a series of experiments. Ten healthy research participants were recruited into a study that evaluated the effects of event-related NMES, whereas 15 healthy research participants were enrolled in a study that investigated the effects of non-event-related NMES. In a third cohort of 35 healthy research participants, task-dependent differences in corticobulbar excitability were evaluated

during three conditions of submental muscle contraction: VC, VPS and submental muscle contraction during the pharyngeal phase of reflexive swallowing (RPS, reflexive pharyngeal swallowing).

Event-related NMES induced frequency-dependent changes in corticobulbar excitability. NMES administered at 80 Hz facilitated MEP amplitude, whereas NMES at 5 Hz and 20 Hz inhibited MEP amplitude. No changes were observed after NMES at 40 Hz. Maximal excitatory or inhibitory changes occurred 60 min post-treatment. Changes in MEP amplitude in response to event-related NMES were only observed when MEPs were recorded during the VC condition, whereas MEPs recorded during the VPS condition remained unaffected. Non-event-related NMES did not affect MEP amplitude in either of the muscle contraction conditions. Similarly, MEP onset latencies remained unchanged across all comparisons. MEPs were detected most consistently during the VC contraction condition. They were less frequently detected and were smaller in amplitude for the VPS condition and they were infrequently detected during pre-activation by RPS.

The documented results indicate that event-related NMES has a more substantial impact on MEP amplitude than non-event-related NMES, producing excitatory and inhibitory effects. Comparison of MEPs recorded during VC, VPS and RPS suggests that different neural networks may govern the motor control of submental muscle activation during these tasks. This research programme is the first to investigate the effects of various NMES treatment protocols on the excitability of submental corticobulbar projections. It provides important new information for the use of NMES in clinical rehabilitation practices and our understanding of the neural networks governing swallowing motor control.

Preface

This PhD thesis is presented according to the referencing style recommended by the American Psychological Association Publication Manual (5th ed.). Spelling adheres to the format recommended by the New Oxford Dictionary for Writers and Editors (2005).

This swallowing neurophysiology research programme was undertaken at the University of Canterbury Swallowing Rehabilitation Research Laboratory, located at the Van der Veer Institute for Parkinson's and Brain Research, Christchurch New Zealand between April 2006 and April 2009. This research was supervised by Dr Maggie-Lee Huckabee, University of Canterbury, and Associate Professor John Dalrymple-Alford, University of Canterbury. This thesis is a continuation of a pilot investigation, which was undertaken in 2005 by Dr Maggie-Lee Huckabee and Sebastian Doeltgen (research assistant). This pilot study was supported financially by a small project grant (0415-SPG) awarded by the Neurological Foundation of New Zealand to Dr. Huckabee. The University of Canterbury Swallowing Rehabilitation Research Laboratory funded research expenses for the NMES treatment investigations. Further financial assistance was provided to Sebastian Doeltgen through a University of Canterbury Doctoral Scholarship, the Departments of Communication Disorders and Psychology (University of Canterbury) and travel grants-in-aide awarded by the Canterbury Medical Research Foundation and Neurological Foundation of New Zealand.

Preliminary results of this research programme have been presented at the following national and international conferences:

- Annual Meeting of the Health Research Society of Canterbury (Christchurch, New Zealand, 24th September 2008)
- Australasian Winter Conference on Brain Research AWCBR (Queenstown, New Zealand, 23rd to 27th August 2008; awarded travel grant in aide)
- Annual Meeting of the Dysphagia Research Society (Charleston, SC, U.S.A., 5th to 8th March 2008; awarded 2nd place New Investigator Award)
- International Brain Research Organization IBRO World Congress of Neuroscience, Satellite Meeting (Darwin, Australia, 18th to 21st July 2007)

Research documented in this thesis has been prepared as the following

publications:

- Doeltgen, S. H., Ridding, M. C., O’Beirne, G. A., Dalrymple-Alford, J., & Huckabee, M. L. (2009). Test-retest reliability of motor evoked potentials (MEPs) at the submental muscle group during volitional swallowing. *Journal of Neuroscience Methods*, 178, 134- 137.
- Doeltgen, S. H., Huckabee, M. L., & Dalrymple-Alford, J. (2008). Influence of Muscle Contraction on Motor Evoked Potentials of the Submental Muscle Group [Abstract]. Retrieved on 7th February 2009 from <http://psy.otago.ac.nz/awcbr/Abstracts2008.htm#Doeltgen>. Paper presented at the Australasian Winter Conference on Brain Research AWCBR, Queenstown, New Zealand.
- Doeltgen, S. H., Huckabee, M. L., & Dalrymple-Alford, J. (2008). Muscle Contraction Influences Motor Evoked Potentials of the Submental Muscle Group Differentially [Abstract]. *New Zealand Medical Journal*. In press. Paper presented at the Annual Meeting of the Health Research Society of Canterbury, Christchurch, New Zealand.
- Doeltgen, S. H., Huckabee, M. L., Dalrymple-Alford, J., Ridding MC, & O’Beirne, G. A. (2009). Effects of Event-related Electrical Stimulation on Motor Evoked Potentials at the Submental Muscle Group [Abstract]. *Dysphagia*, 23, 436. Paper presented the Annual Meeting of the Dysphagia Research Society, Charleston, SC, U.S.A.
- Doeltgen, S. H., Huckabee, M. L., & Ridding, M. C. (2009). A Pilot Investigation of Triggering Methods for Motor Evoked Potentials of the Submental Muscle Group [Abstract]. *Dysphagia*, 23, 454. Poster session presented at the Annual Meeting of the Dysphagia Research Society, Charleston, SC, U.S.A.
- Doeltgen, S. H., Huckabee, M. L., & Ridding, M. C. (2007). A Pilot Investigation of Triggering Methods for Motor Evoked Potentials at the Submental Muscle

- Group [Abstract]. “*Motor Control at the Top End*” 2007 IBRO World Congress of Neuroscience Satellite Meeting. M. C. Ridding & S. Gandevia (Eds). Eastwood, SA.
- Huckabee, M. L., & Doeltgen, S. H. (2007a). Position Paper of the New Zealand Speech Therapists’ Association (NZSTA) on Neuromuscular Electrical Stimulation in Dysphagia Management. Retrieved on 16th March 2009 from <http://www.speechtherapy.org.nz/information-for-speech-and-language-therapists>
- Huckabee, M. L., & Doeltgen, S. H. (2007b). Emerging Modalities in Dysphagia Rehabilitation: Neuromuscular Electrical Stimulation. *The New Zealand Medical Journal*, 120, 1-9.
- Other publications completed during MSLT and PhD studies at the University of Canterbury between February 2005 and March 2009:
- Doeltgen, S. H., Witte, U., Gumbley, F., & Huckabee, M. L. (2009). Evaluation of Manometric Measures During Tongue-hold Swallows. *American Journal of Speech and Language Therapy*, 18, 65-73.
- Huckabee, M. L., & Doeltgen, S. H. (2009). Die Entwicklung von Rehabilitationsansätzen für pharyngeale Bewegungsstörungen: Die Verknüpfung von Forschung und Klinischer Arbeit. In: A. Hofmayer & S. Stanschus (Eds.), *Development of evidence in Dysphagiology: from screening to treatment*. Idstein, Schulz-Kirchner. Chapter in press.
- Gumbley, F., Huckabee, M. L., Doeltgen, S. H., Witte, U., & Moran, C. (2008). Effects of Bolus Volume on Pharyngeal Contact Pressure during Normal Swallowing. *Dysphagia*, 23, 280-285.
- Witte, U., Huckabee, M. L., Doeltgen, S. H., Gumbley, F., & Robb, M. (2008). The Effect of Bolus on Pharyngeal Manometric Pressure Measurements in Effortful and Non-Effortful Swallowing in Healthy Participants. *Archives of Physical Medicine and Rehabilitation*, 89, 822-828.
- Doeltgen, S. H., Hofmayer, A., Gumbley, F., Witte, U., Moran, C., Carroll, G., & Huckabee, M. L. (2007). Clinical measurement of pharyngeal surface electromyography: exploratory research. *Neurorehabilitation and Neural Repair*, 21, 250-262.
- Doeltgen, S. H., Huckabee, M. L., Witte, U., & Gumbley, F. (2007). Pharyngeal Pressure Generation During Tongue-hold Manoeuvre [Abstract]. *Dysphagia*, 22, 374. Poster session presented at the Annual Meeting of the Dysphagia Research Society in Vancouver, Canada.

PART I

Chapter 1: Introduction

Since the turn of the millennium, neuromuscular electrical stimulation (NMES) has become a novel and increasingly popular tool in the therapeutic repertoire of speech language therapists. A number of studies have since documented contradicting results regarding the effects of this treatment on oropharyngeal swallowing biomechanics and swallowing safety. Positive outcomes reported in patients with dysphagia in response to NMES treatment include increased laryngeal elevation (Leelamanit, Limsakul & Geater, 2002) and subjective ratings of improved swallowing function (Freed, Freed, Chatburn & Christian, 2001; Blumenfeld, Hahn, LePage, Leonard & Belafsky, 2006). Other research groups have reported no significant changes in electromyographic activity of the stimulated muscles (Burnett, Mann, Stoklosa & Ludlow, 2005; Suiter, Leder & Ruark, 2006), descent of the hyo-laryngeal complex during treatment in healthy volunteers (Humbert, Poletto, Saxon, Kearney, Crujido, Wright-Harp et al., 2006) and volunteers with swallowing problems (Ludlow, Humbert, Saxon, Poletto, Sonies & Crujido, 2007), and no significant improvement in pharyngeal swallowing biomechanics in individuals with swallowing disorders (Kiger, Brown & Watkins, 2006). Stimulus parameters employed during NMES varied widely across studies, with NMES stimulus frequencies ranging from 0.2 Hz (Power, Fraser, Hobson, Rothwell, Mistry, Nicholson et al., 2004) to 80 Hz (Freed et al., 2001; Ludlow et al., 2006; Kiger et al., 2006; Blumenfeld et al., 2006; Humbert et al., 2006). Further, NMES duration varied from 5 min in experimental research on healthy individuals (Fraser, Power, Hamdy, Rothwell, Hobday, Hollander et al., 2002; Power et al.,

2004) to 4 hrs (Leelamanit et al., 2002) in clinical research. Although a NMES treatment device, marketed as Vitalstim™, is available for application in swallowing rehabilitation, the lack of a clearly defined treatment protocol, which is based on thorough empirical research, is of primary concern and the basis of international discussion.

The task context during which NMES is administered may exert an additional influence on the effects evoked by this treatment. Research in other areas of rehabilitation medicine suggests that NMES administered during performance of a purposeful task may yield greater functional benefits than NMES administered to muscles at rest (Bax, Staes & Verhagen, 2005; Glanz, Klawanski, Stason, Berkey & Chalmers, 1996; Bolton, Cauraugh & Hausenblas, 2004). Except for one clinical treatment study (Leelamanit et al., 2002) and three basic research studies evaluating the immediate effects on swallowing biomechanics (Burnett et al., 2005; Ludlow et al., 2006; Humbert et al., 2006), all other swallowing research has administered non-event-related NMES. A direct comparison of the biomechanical and neurophysiological effects of event-related and non-event-related NMES administered to the muscles involved in swallowing remains outstanding.

Limited data are available regarding the effects of NMES on measures of swallowing neurophysiology. Research into the effects of NMES on motor evoked potentials (MEPs), a measure of the excitability of corticobulbar projections, has documented that changes are frequency-specific with optimal stimulation parameters differing for varying anatomical sites. In healthy research participants, Fraser et al. (2002) documented that MEP amplitude recorded from the muscles underlying the pharyngeal mucosa increased at 5 Hz and decreased at 20 and 40 Hz compared to pre-treatment baseline. Power et al. (2004) documented similar frequency-specific findings after NMES of the muscles underlying the faucial pillars in healthy

participants, although 0.2 Hz NMES was documented to be excitatory, whereas 5 Hz NMES resulted in inhibition of MEPs. Importantly, effects on MEP amplitude were related to changes in swallowing function, with greater corticobulbar excitability correlating with improved swallowing function and vice versa.

Based on these findings, one can presume that optimal stimulation parameters exist for other muscles involved in the act of swallowing, for example the anterior hyo-laryngeal (submental) muscle group. For this muscle group, these parameters are yet to be identified. Clinical applications of the research findings by Fraser et al. (2002) and Power et al. (2004) are limited, as the musculature underlying the pharyngeal mucosa or faucial pillars is clinically not readily accessible. Identification of optimal NMES parameters for the more easily accessible submental muscle group is therefore imperative and pressing, since it is already a common target for the application of NMES in swallowing rehabilitation practices. Further, in the abovementioned studies MEPs were recorded while the target muscles were at rest. Evaluation of MEPs recorded during purposeful muscle pre-activation would provide insight into the excitability of corticobulbar projections in a functional context.

The primary objective of this research programme was to establish optimal NMES stimulation parameters for the submental muscle group, as identified by increased excitability of corticobulbar projections. This research programme is based on previously documented methodologies (Fraser et al., 2002; Power et al., 2004), which evaluated changes in MEP amplitude and onset latency in response to NMES in order to identify optimal stimulation parameters for the musculature underlying the pharyngeal or faucial pillar mucosa. The methodological design was improved upon by providing event-related NMES and by recording MEP outcome measures in a task-related context, that is, during volitional muscle contraction (VC)

and muscle contraction during the pharyngeal phase of volitional swallowing (volitional pharyngeal swallowing, VPS). The evaluated parameters included electrical stimulus frequency and overall dose of NMES administered, which varied by differing duration of the NMES stimulus or differing the number of stimulus train repetitions. The significance of the task context during which NMES is administered was evaluated by comparing changes in corticobulbar excitability in response to event-related and non-event-related NMES, administered at the optimal stimulation parameters identified in the previous studies.

Prior to the evaluation of optimal stimulus parameters, three methodological pilot investigations were undertaken to (a) evaluate the reliability of MEP amplitude and onset latency recorded during the two muscle pre-activation conditions (VC and VPS), to (b) investigate differences in MEP amplitude and onset latency measures recorded during VC, VPS and submental muscle contraction during the pharyngeal phase of reflexive swallowing (reflexive pharyngeal swallowing, RPS) and to (c) identify the influences of repeated volitional swallowing and time on the excitability of corticobulbar projections to the submental muscle group.

Presented in this thesis are data recorded from healthy adults between the ages of 20 and 47 yrs. Analyses were performed in the context of three pilot investigations (Parts III and IV), and established the effects of event-related NMES (Part V) and non-event-related NMES (Part VI) on the excitability of submental corticobulbar projections. Results are discussed in reference to previous research into swallowing neurophysiology and the effects of NMES interventions on neural substrates and biomechanics of swallowing. The implications of these findings on our understanding of swallowing motor control and on the clinical application of NMES are also discussed.

Chapter 2: Swallowing Neurophysiology

Swallowing is a complex neuroanatomical process, which requires the precise coordination of 32 paired muscles involved in the movement of the jaw, lip, tongue, soft palate, pharynx and upper oesophageal sphincter (UOS) (Guyton, 1986). These muscles are innervated by five cranial and two cervical nerves (Perlman & Christensen, 1997). The act of swallowing can be separated into oral preparatory, oral, pharyngeal and oesophageal phases (Logemann, 1997)¹. These phases may be preceded by a multi-sensory pre-oral phase, during which the situational context of deglutition, and gustatory, olfactory and other related sensory stimuli are processed. The oral phase is primarily under voluntary control and is responsible for the initial containment of all bolus types and the preparation of solid foods to be ingested through chewing and formation of a soft, cohesive bolus (Logeman, 1997). The pharyngeal phase of swallowing is initiated by the arrival of the prepared bolus from the oral cavity in the pharynx and is coordinated by a complex innervation pattern employing brainstem, but also cortical, neural networks. This phase lasts approximately 800 ms (McConnel, Cerenko, Jackson & Griffin, 1988), during which the tongue propels the bolus into the pharynx, the epiglottis deflects and covers the laryngeal entrance and the vocal folds adduct. At the same time, the UOS relaxes and is pulled open by concomitantly occurring anterior-superior hyo-laryngeal elevation, which is a result of the contraction of the anterior hyo-laryngeal musculature (submental muscle group) (Logemann, 1983). Through retraction of base of tongue (BOT) and other anterior structures and peristaltic-like contraction of the pharyngeal musculature, the bolus is propelled

¹ It is noteworthy that the division into phases serves the purpose of conceptualising the complex sensorimotor sequence of swallowing. It does not represent a separation of the closely linked neurophysiological and biomechanical events that underlie the swallowing motor response.

through the open UOS into the oesophagus (Morrell, 1984). The oesophageal phase is under reflexive control of brainstem neural networks, in particular those of the nucleus ambiguus (NA), and is responsible for transporting the swallowed bolus caudally into the stomach (Diamant, 1989).

This precisely orchestrated chain of events is achieved by sequenced muscle contraction through innervation via afferent and efferent cranial nerves, including the trigeminal, glossopharyngeal, facial, vagus nerves and hypoglossal nerves, in addition to the purely efferent ansa cervicalis [hypoglossal nerve and the first two cervical nerves (C1 & C2)] (Perlman & Christensen, 1997). Besides the obvious objective of transporting bolus from the oral cavity to the stomach, the pharyngeal phase serves the additional, and equally important, purpose of protecting the airway during the pharyngeal bolus passage. Airway protection relies heavily on the precisely timed integration of afferent sensory feedback from the laryngeal structures, and motor output via efferent motor nerves. Sensory feedback is conveyed from the larynx, pharynx, and epiglottis via the internal branch of the superior laryngeal nerve (SLN) of the vagus, the facial nerve (soft palate and adjacent pharyngeal wall), and glossopharyngeal nerve (base of tongue (BOT) and upper pharynx) to the nucleus tractus solitarius (NTS) (Perlman & Christensen, 1997). Sensory information from areas below the vocal folds is conveyed via the recurrent laryngeal branch of the vagus nerve. The motor fibres of this nerve innervate the muscles responsible for laryngeal closure and indirectly deflection of the epiglottis (Perlman & Christensen, 1997). Efferent innervation to the submental musculature, involved in superior-anterior displacement of the hyo-laryngeal complex during swallowing, occurs via the trigeminal nerve (mylohyoid and anterior belly of digastric muscles) and the ansa cervicalis (geniohyoid muscle). The

stylohyoid muscles, involved in superior-posterior hyo-laryngeal elevation, are innervated by the motor branch of the facial nerve.

The nuclei of the afferent and efferent cranial nerves involved in swallowing are located in the brainstem. Afferent sensory information converges either directly or indirectly on the nucleus tractus solitarius (NTS), located in the dorsal medulla, deeming it particularly important for the initiation and excitatory or inhibitory modulation of the swallowing motor sequence (Jean, 2001). The execution of the motor sequence is orchestrated by switching neurons located in the nucleus ambiguus (NA) in the ventrolateral medulla, which distribute the swallowing motor plan either directly or indirectly to the various motor neuron pools of the cranial nerves (Jean, 2001).

Electrical stimulation of the SLN, and the NTS directly, has been shown to induce swallowing, underscoring the importance of sensory feedback in the initiation of the swallowing motor sequence. Interestingly, electrical stimulation of the pericentral cortices, has also been shown to induce swallowing in animals and humans (Car, 1970; Miller & Bowman, 1977). This observation is supported by clinical reports of swallowing impairment resulting from hemispheric damage (Robbins, Levine, Maser, Rosenbek & Kempster, 1993).

However, cortical and subcortical regions activated during swallowing are not essential for the coordination of a physiologic swallowing response (Miller & Bowman, 1977). It has been shown that human foetuses are capable of swallowing from the 12th gestational week, long before cortical and subcortical structures are developed (Hooker, 1954). Anencephalic human foetuses are also reported to be capable of swallowing (Pritchard, 1965; Peleg & Goldman, 1978). It has further been documented that intra-oral stimulation of decerebrate animals can induce licking, chewing and pharyngeal swallowing behaviour (Doty & Bosma, 1956). This

is strong evidence for how imperative brainstem neural networks are for the control of swallowing. In recent years, however, mounting evidence has been presented that cortical regions may also play an important role in the central neural control of swallowing.

2.1: Cortical Control of Swallowing

The contributions of the primary motor cortex and other cortical areas to the neural control of swallowing have been implicated by several studies employing a variety of neurophysiological assessment techniques [see review by Hamdy (2006)], but the precise extent and functional relevance have not yet been clearly defined. The pharyngeal phase of swallowing has been thought to be mediated principally by brain stem mechanisms with little cortical involvement (Jean, 2001). Research has indicated, however, that reflexive swallowing may also be subject to excitatory or inhibitory regulation by descending cortical pathways (Kern et al., 2001a). The exact nature of this regulation and the role of different cortical regions activated during volitional and reflexive swallowing in the planning and execution of these tasks remain largely unknown. Advancing developments in brain imaging technology have enabled researchers to gain an increasing understanding of the role of cortical areas in the control of both unimpaired and disordered swallowing. Such techniques include functional magnetic resonance imaging (fMRI) (Martin, Goodyear, Gati & Menon, 2001; Martin, MacIntosh, Smith, Barr, Stevens, Gati et al., 2004; Hamdy, Mikulis, Crawley, Xue, Lau, Henry et al., 1999a; Toogood, Barr, Stevens, Gati, Menon & Martin, 2005; Kern, Jaradeh, Arndorfer & Shaker, 2001a; Kern, Birn, Jaradeh, Jesmanowicz, Cox, Hyde et al., 2001b), transcranial magnetic stimulation (TMS) (Hamdy, Aziz, Rothwell, Hobson & Thompson, 1998a; Fraser et al., 2002), positron emission tomography (PET) (Zald & Pardo, 1999; Hamdy, Rothwell,

Brooks, Bailey, Aziz & Thompson, 1999b), electroencephalography (EEG) (Huckabee, Deecke, Cannito, Gould & Mayr, 2003; Satow, Ikeda, Yamamoto, Begum, Thuy, Matsushashi et al., 2003) and magnetoencephalography (MEG) (Dziewas, Soeroes, Ishii, Chau, Henningsen, Ringelstein et al., 2003).

Activation of multiple cortical sites has been identified during volitional bolus and saliva swallowing. These areas include the primary motor (M1) and sensory areas (S1) (Hamdy et al., 1999a; Martin et al., 2001; Kern et al., 2001a; Kern et al., 2001b; Martin et al., 2004; Toogood et al., 2005), the anterior cingulate cortex (ACC) (Martin et al., 2001; Kern et al., 2001a; Kern et al., 2001b; Martin et al., 2004; Toogood et al., 2005), premotor areas (Hamdy et al., 1999a; Kern et al., 2001b), the insular cortex (Kern et al., 2001a; Kern et al., 2001b; Martin et al., 2001), occipitoparietal areas (Hamdy et al., 1999a; Kern et al., 2001a; Kern et al., 2001b), the frontoparietal operculum (Hamdy et al., 1999a; Martin et al., 2004) and the supplementary motor area (SMA) (Huckabee et al., 2003; Satow et al., 2003; Martin et al., 2004). Neuroimaging studies consistently report multifocal activation during swallowing, however, the precise role of these areas in swallowing motor control remains unknown. There is particular discussion around the involvement of M1 in the motor control of swallowing. A number of studies have reported activation in the caudolateral part of this region (Hamdy et al., 1999a; Martin et al., 2004), which has been shown to contain motor representations for the face and tongue (Penfield & Jasper, 1954). The particular role of this area in the swallowing motor sequence, however, has not been clearly defined. Specifically, it is unknown whether the activation documented for this site relates to voluntary oral movement during bolus preparation and transport, reflexive pharyngeal or oesophageal motor components, or a combination of both.

In an attempt to elucidate the contribution of the M1 to swallowing motor control, Kern et al. (2001b) compared cortical activation during functional motor tasks related to volitional swallowing, including lip pursing, tongue rolling and jaw clenching, to cortical activation during volitional saliva swallowing. Data from 14 young healthy research participants revealed multifocal activation of the anterior cingulate gyrus, the motor and premotor cortices, the insular cortex and occipitoparietal areas during the volitional swallowing task. The primary motor area found to be activated during the swallowing-related motor tasks was also activated during volitional swallowing, indicating a contribution of M1 to different, but related, motor tasks. In this study, signal intensity, representing the degree of cortical activation, was similar for volitional swallowing and swallowing-related movements. The documented similarities in cortical activation therefore indicate that cortical regions involved in the control of voluntary, swallowing-related motor tasks may also be actively involved in the motor control of volitional swallowing. However, the interpretation of these data is limited by the fact that research participants were not instructed to limit oral preparatory movement prior to pharyngeal swallowing. This may have introduced a volitional motor component to the swallowing task, which resembles motor cortical activation during the voluntary oral motor tasks. Due to the limited temporal resolution of fMRI, cortical activation related to voluntary oral movements cannot be distinguished from cortical activation related to movements during the reflexive pharyngeal phase of swallowing. The authors further state that the large voxel size used in this study may have prevented identification of differences in cortical activation during volitional swallowing and swallow-related movements.

While Kern et al. (2001b) documented no differences in the level of activation between volitional swallowing and swallow-related motor tasks, Martin et

al. (2004) reported greater activation of cortical volume, including M1, during volitional tongue elevation compared to volitional swallowing. In this study, 14 young healthy research participants underwent event-related fMRI while performing a visually cued volitional swallowing task and a voluntary tongue elevation task. To explain the greater cortical activation during the tongue elevation task, the authors hypothesised that tongue elevation may require overall a greater motor effort than swallowing, thus activating a greater cortical volume. Alternatively, the authors suggested “the differential cortical activation for swallowing and tongue movement may reflect the fact that much of the processing for swallowing is mediated by brain stem mechanisms, whereas regulation of voluntary movements relies more heavily on cortical/subcortical networks” (Martin et al., 2004, p. 2440). This view is in line with previous research that has shown that brainstem pattern generators may be primarily responsible for the motor execution of pharyngeal swallowing (Jean, 2001). Other common areas of activation were the frontoparietal operculum and the anterior cingulate cortex, indicating that these areas may be involved in sensorimotor processing of different, but related functional contexts. In addition, greater activation of the SMA and premotor cortex were documented during the tongue elevation task. This finding is particularly interesting, as prior research has documented a positive relationship between the degree of SMA activation and voluntary motor task complexity (Toyokura, Muro, Komiya & Obara, 2002). Therefore, greater activation of cortical structures involved in pre-motor planning would have been expected during the more complex swallowing task. This finding can be interpreted in support of the above stated hypothesis that volitional swallowing relies less heavily on cortical motor control than voluntary oral movements. As in the study by Kern et al. (2001b), interpretation of the precise role of the documented cortical activation foci during pharyngeal swallowing is limited,

because activation may in large part relate to oral preparatory movements or central processing of the visual cue to perform the tasks or other sensory inputs.

In a subsequent study, Toogood et al. (2005) investigated cortical activation during a visually cued “go” (do swallow) and “no go” (don’t swallow) paradigm. This study was undertaken to overcome the methodological limitations of earlier research by differentiating between cortical activation foci associated with swallowing and cortical processing of the visual cue. In five regions of interest, cortical activation was significantly greater during the “go” condition compared to the “no go” condition in all 8 participants: the precentral gyrus, the postcentral gyrus, the anterior cingulate gyrus corresponding to BA24 (Brodmann’s area 24) and BA32, and the insular cortex. In fact, activation occurred exclusively during the “go” condition in the precentral gyrus in 4 of 8 participants and in the postcentral gyrus in 5 of 8 participants. In contrast, activation of the cuneus and precuneus did not differ between the two conditions. These findings were interpreted to suggest that M1 and S1 are specifically involved in execution of swallowing, whereas the cuneus and precuneus regions are involved in the processing of the visual cue provided in this research paradigm. These findings support earlier research that has documented activation of M1 during volitional swallowing (Hamdy et al., 1999a; Martin et al., 2001; Kern et al., 2001b). The anterior cingulate cortex documented to be active during volitional swallowing in this and other studies (Kern et al., 2001b) has been suggested to contribute to movement planning and execution, or processes such as the level of attention (Kern et al., 2001b). Greater activation of this area during the “go” condition in this study suggests that this cortical region may be directly related to the act of swallowing, rather than the processing of the experimental environment. While this study was able to distinguish between cortical areas that were predominantly activated during volitional swallowing and those

related to processing of the visual cue, the precise role of the swallowing-related activation foci in the complex planning and execution sequence of swallowing remain to be clearly defined. The temporal resolution of fMRI substantially limits the identification of sequential activation of cortical areas; thus, other brain imaging techniques may contribute important information about the role of cortical activation foci, particularly M1, in the neural control of swallowing.

Research employing EEG has contributed important information to the interpretation of the data reported by fMRI investigations. Huckabee et al. (2003) investigated cortical motor planning prior to a task in which participants were specifically instructed to inhibit orolingual movements before volitional onset of pharyngeal swallowing. Evaluation of the Bereitschaftspotential (BP, or readiness potential) during this task allowed isolated evaluation of cortical activation in the premotor planning phase of the pharyngeal swallow. The Bereitschaftspotential is a gradually rising negative potential, which occurs approximately 1.5 s prior to voluntary movements. Its first component (BP1) precedes volitional movement by approximately 1 to 1.5 s and reflects bilateral cortical activation in the SMA. Its second component (BP2) occurs 0.5 s prior to movement onset and shifts towards the contralateral side to movement, reflecting activation of the unilateral M1 (Deecke & Kornhuber 1978). Based on the findings reported by fMRI studies, one would thus expect that the BP be measurable before volitional swallowing. Indeed, the first component of the BP was identified prior to volitional swallowing (Huckabee et al., 2003). However, the second component of the BP, which is known to correlate with transfer of the motor plan from SMA to M1, was absent. The authors hypothesised that this relative inactivity represented the neural command generated by the SMA being directly sent to the swallowing pattern generators in the brainstem. This finding is in agreement with prior reports of absent BPs before

reflexive or passive movement (Regan, 1989). In a similar study of cortical potentials in eight healthy research participants, Satow et al. (2003) reported comparably large BPs, but lower post-movement potentials, for volitional swallowing compared to a tongue protrusion task. This suggests that the role of the cortex in the premotor planning stages is similar for the two tasks, but that its contribution to movement processing is substantially less for volitional swallowing. The combined results of these EEG studies therefore suggest that the activation of M1 documented in prior fMRI investigations likely does not relate to the motor control of the pharyngeal phase of swallowing, but voluntary oral movements. It is noteworthy that the methodology employed in the study by Huckabee et al. (2003) may have affected the shape of the BP. Inhibition of oral movement and the difficulty of the isolated pharyngeal swallowing task may have introduced a relative positivity in the recorded BP measures, thus affecting the negative BP waveform associated with volitional movements.

In light of the reports of a relative quiescence of M1 during the reflexive pharyngeal phase of volitional swallowing, fMRI evaluation of cortical activity during reflexive swallowing is of particular interest. As stated above, the initiation and execution of the volitional swallowing tasks performed in previous fMRI studies requires a large degree of volitional effort from the research participant. It can therefore be argued that the volitional nature of these motor tasks, more specifically those of preparatory tongue movements in the oral phase, is primarily responsible for the activation observed in primary sensorimotor areas. It would be expected that cortical activation during non-volitional swallowing would decrease or even be entirely absent. This hypothesis is in line with the findings reported by investigations of premotor planning employing EEG. Two research groups have

attempted to elucidate this question by investigating cortical activation in a volitional swallowing task compared to reflexive or automatic swallowing.

Kern et al. (2001a) investigated cortical activation during volitional swallowing and a reflexive swallowing task in 8 young healthy research participants who performed 30 repetitions of volitional saliva swallows (cued by a tap on the leg) and reflexive swallowing (evoked by infusion of a small water bolus into the oropharynx). An event-related data acquisition paradigm was used with single swallow trials intermittently performed with 30 s rest periods. Interestingly, reflexive swallowing resulted in bilateral cortical activation, primarily of the primary sensorimotor areas. In agreement with previous studies, volitional swallowing additionally activated the insular cortex, and prefrontal, anterior cingulate and parieto-occipital regions. Within participants, the total volume of activated voxels was greater during volitional than reflexive swallowing. Activation of primary sensorimotor areas during both volitional and reflexive swallowing was interpreted to reflect the previously reported similarities in biomechanical events documented for volitional and reflexive swallows (Shaker, Ren, Zamir, Sarna, Liu & Sui, 1994). The authors concluded that the additional regions activated during volitional swallowing, in particular the prefrontal cortex, anterior cingulate cortex and insular cortex, “may represent the volitional aspect of the swallowing such as intent, planning, and possibly urge” (Kern et al., 2001a, p. 359). Even though the reflexive swallowing task in this study was induced without volitional effort of the research participant, the predictable infusion of water into the oropharynx may have resulted in anticipatory movements of the tongue and the pharyngeal musculature, which may in turn explain the observed activation of primary motor areas during this swallowing condition, and thus limit the interpretation of these data. A further problem with the reflexive swallowing protocol is the fact that a water bolus is

infused into the pharynx. While this may be a necessary prerequisite for eliciting a reflexive swallow, this method introduces several degrees of freedom to the paradigm, including sensory input from the water bolus and an increased level of arousal to facilitate airway protection.

Martin et al. (2001) used a less “invasive” paradigm by comparing cortical activation during volitional swallowing and water bolus swallowing to that observed during automatic swallowing. Automatic swallowing was defined as swallowing that occurred without the conscious awareness of the research participant. Fourteen young healthy research participants were investigated, with fMRI scans evaluating automatic swallows, followed by a series of volitional saliva swallows and 3 ml water bolus swallows. All three swallowing conditions resulted in activation of the lateral primary sensorimotor areas and the right insula. The caudal anterior cingulate cortex, associated with the processing of sensory, motor and cognitive information (Devinsky, Morrell & Vogt, 1995) was significantly more activated during the volitional swallowing conditions (saliva and 3 ml bolus) than during the automatic swallowing condition. Asymmetrical activation of the sensorimotor cortex, with greater activation of the left hemisphere, occurred in 9 of 12 participants for the automatic swallows, in 6 of 14 participants for the volitional swallows and in 7 of 13 participants for the bolus swallows. For all except 1 participant, lateralisation depended on the task performed and changed from one hemisphere to the other for one of the three conditions within participants.

These data provide support for the view that both volitional and automatic swallowing involves cortical activation, in particular in the primary sensorimotor areas and the right insula. It may be argued, however, that the automatic swallows investigated in this study were not entirely naïve, as participants were aware they were participating in a study that investigated swallowing and were asked to remain

relaxed without “altering their vegetative functions such as breathing and swallowing” (Martin et al., 2001, p. 940). This may have drawn their attention to these functions, inadvertently introducing a volitional component to the “automatic” swallowing condition.

Despite methodological limitations, these two studies indicate that some cortical regions, in particular the primary motor and sensory cortices, may not be exclusively activated during volitional swallowing tasks, but also during reflexive or automatic swallowing. These findings expand on earlier research in decerebrate or anaesthetised animals, which documented that electrical stimulation of the pharyngeal and laryngeal mucosa (Dubner, Sessle & Storey, 1978) or the superior laryngeal nerve (Miller, 1972) can induce swallowing, suggesting that brainstem networks suffice to initiate swallowing. These results are in contrast to BP studies, which documented a relative quiescence of M1 during the reflexive pharyngeal phase of swallowing. Some cortical regions were exclusively activated during volitional swallowing (e.g. the insula, cingulate gyrus, cuneus and precuneus), indicating that “the activation of non-sensory/motor cortical regions observed in volitional swallowing probably represents the volitional aspects of the swallow such as intent, urge, decision making, and memory, as well as information processing related to deglutition” (Kern et al., 2001a, p. 358).

Other brain imaging modalities such as PET and MEG have contributed further information about cortical activation foci during swallowing. PET has been successfully used to investigate cortical blood flow during volitional saliva (Zald & Pardo, 1999) and water swallowing (Hamdy et al., 1999b). Activation of the lateral sensorimotor cortices was documented for both types of swallows, with some activation also documented in the right insula and cerebellum (Zald & Pardo, 1999; Hamdy et al., 1999b). Further, inconsistent activation was documented in the

putamen and thalamus during saliva swallowing (Zald & Pardo, 1999) and left premotor cortex, brainstem and amygdala during water swallowing (Hamdy et al., 1999b). In most participants, one hemisphere showed greater activation in the primary motor and sensory cortices during the water swallows, opposed to only 25% of participants during saliva swallows. These results are in agreement with those reported by fMRI studies, in that (a) activation was multifocal, including the primary sensorimotor areas and (b) activation was asymmetrically stronger in one hemisphere in some individuals. The latter finding is supported by studies employing TMS. Lateralised dominance was indicated by larger MEPs recorded from the pharyngeal and oesophageal musculature when TMS was performed over the “dominant” hemisphere (Hamdy, Aziz, Rothwell, Power, Singh & Nicholson, 1998b). Further evidence for hemispheric dominance can be gleaned from fMRI studies reporting unequal hemispheric activation during swallowing (Martin et al., 2004; Kern et al., 2001a).

As with research employing fMRI, PET has poor temporal resolution, prohibiting analysis of sequential cortical activation during swallowing. This limitation is overcome with MEG, which has a much higher temporal resolution and is capable of detecting cortical activation in a more sequential manner. This is particularly useful for investigating the sequencing of cortical activity during the rapid succession of oropharyngeal events during swallowing. Abe, Wantanabe, Shintani, Tazaki, Takahashi, Yamane et al. (2003) documented bilateral activation of the anterior cingulate gyrus and the supplementary motor area at 1 to 1.5 s before the onset of volitional water swallowing. Activation of the cingulate gyrus occurred only very briefly, and ceased prior to the onset of muscle activation, suggesting a role in the initiation and cognitive processing of swallowing. In the pre-motor planning phase (1.5 s before movement onset), both volitional swallowing and a

tongue movement task (tongue press against hard palate) resulted in activation of bilateral primary sensorimotor cortices, whereas no activation was observed prior to reflexive swallowing (evoked by injection of small amounts of water directly into the pharynx) (Dziewas et al., 2003). This observation is of particular interest, as one would expect that activation of M1 occurs during, rather than prior to, motor execution.

During volitional swallowing and tongue movement, activation was observed in the mid-lateral primary motor and sensory cortices, whereas reflexive swallowing activated more medial parts of the primary sensorimotor cortex. This observation is in line with previous research reporting a distinct somatotopical distribution of oral and pharyngeal muscles on the motor cortex (Hamdy, Aziz,, Singh, Barlow, Hughes, Tallis, et al., 1996). Strong lateralisation to the left hemisphere occurred during volitional swallowing, which was less pronounced during reflexive swallowing and absent during the tongue movement task (Dziewas et al., 2003). This finding supports prior research using fMRI (Kern et al., 2001b) and “may reflect the more pronounced cortical control of volitionally initiated movements as compared to reflexive movements” (Dziewas et al., 2003, p. 139). It was hypothesised that lateralisation of cortical activation may be a function of the complexity of the performed movement. Bilateral activation observed in the premotor planning phase and lateralised activation during motor execution was interpreted to reflect greater importance of lateralised function for motor execution, rather than for premotor sensory processing (Dziewas et al., 2003).

2.2: Summary, Limitations and Future Directions

Swallowing is a vital and complex sensorimotor task that requires the precise coordination of a number of oral and pharyngeal biomechanical events. Motor

execution of these events, modulated by peripheral sensory feedback, has been shown to be primarily driven by swallowing central pattern generators located in the brainstem (Jean, 2001). Converging evidence from studies employing a variety of neurophysiological assessments suggests a contribution of cortical neural networks to the planning, initiation and possibly also execution of swallowing. Combined interpretation of the results reported by neuroimaging studies suggests that M1 is activated at some stage during volitional swallowing and during voluntary oral movements that are related to swallowing, and that it may, therefore, contribute to the motor control of these tasks although its precise role and extent have not been clearly defined. Further, M1 may also be activated during reflexive swallowing, however, reports are contradicting. The degree of M1 activation decreases along a continuum of “volitional effort”, being greatest during voluntary movements, less during volitional swallowing and least (or absent) during reflexive swallowing. Finally, studies evaluating M1 activation in the motor planning phase prior to reflexive pharyngeal swallowing have indicated that M1 is not actively involved in this phase, with some researchers suggesting a direct functional connection between SMA and brainstem swallowing pattern generators.

Activation of multiple other regions has been linked to human swallowing, but their specific roles in the modification, sensorimotor integration and execution of swallowing remain unknown. The demonstrated multifocal cortical activation likely explains why swallowing disorders result from a diverse range of cortical insults (Daniels & Foundas, 1997).

Functional brain imaging techniques are limited in their temporal resolution (approximately 4 s for fMRI and 40 s for PET) (Aine, 1995), particularly in regard to the measurement of complex and short-lasting events such as swallowing, which involves the coordination of 32 muscle pairs over a period of only approximately

800 ms (McConnel et al., 1988). Research has identified specific cortical areas that are activated at some point before or during this period; however, their precise timing in the sequencing of swallowing-related neurophysiological events remains difficult. Magnetoencephalography has provided some additional temporal information, however, it is limited in regard to spatial resolution, particularly that of subcortical structures, which would likely also be involved in the control of swallowing (Dziewas et al., 2003). Most studies are further limited by methodological issues, as it is difficult to control for voluntary tongue movements in the oral phase. Movement may create motion artefacts and result in activation of cortical foci that are not directly related to the neural control of pharyngeal swallowing. When reflexive swallowing is studied, factors such as sensory stimulation or the urge to protect the airway from the infused bolus may affect cortical activation.

Transcranial magnetic stimulation provides an alternative assessment tool, since TMS elicited MEPs offer a means of investigating cortical activation at rest or during performance of a motor task. As MEPs are measured within milliseconds after transcranial stimulation, this method offers high temporal resolution for the investigation of cortical excitability. The degree of the excitability of corticobulbar projections is reflected in MEP amplitude (Bestmann, 2007) and its topographical extent can be identified by cortical activation maps (Fraser et al., 2002). In swallowing neurophysiology research, MEPs have been evaluated to investigate corticobulbar motor pathways and map representations, with measurements taken when the muscles of interest were at rest (Hamdy, Aziz, Rothwell, Hobson, Barlow & Thompson, 1997; Hamdy et al., 1998a; Fraser et al., 2002; Power et al., 2004). These investigations have been shown to produce reliable results, as cortical activation maps have been confirmed by fMRI (Fraser et al., 2002). However, the

documented results do not provide insight into the active recruitment of these connections during performance of different motor tasks. Based on the studies reviewed in this chapter, it is plausible that differences exist in the recruitment of the identified neural pathways, depending on the nature of the performed task.

No studies have employed MEPs recorded during muscle pre-activation, in order to study corticobulbar excitability during swallowing-related motor tasks. Precisely timed triggering of TMS, and subsequent MEPs, during the pharyngeal phase of swallowing would provide important insight into the degree of excitability of corticobulbar projections during this phase of swallowing. Further, task-related MEPs could also be employed to evaluate changes in corticobulbar excitability in response to rehabilitative intervention, for example NMES.

Chapter 3: Electrical Stimulation in Rehabilitation

The potential of electrically stimulating human muscle and brain tissues has been documented and evaluated as a treatment approach for a variety of medical conditions for many centuries. Applications have been reported as early as 400 B.C. when Torpedo fish were used to relieve headaches or arthritic pain (Baker, McNeal, Benton, Bowman & Water, 1993). The early basis for the battery-powered electrical stimulators used today was established in 1799, when Alessandro Volta was the first to construct the “voltaic pile”, the forerunner of the battery, which produced a constant electric current. When applied to the muscle, this current induced a contraction at the onset of current flow. The nineteenth century has seen the development and advancement of many inventions, for example Faraday’s current generator or Duchenne’s surface electrodes, which facilitated the application of electrical stimulation as a rehabilitative treatment tool. Over the next century, these inventions progressively led to the implementation of electrical stimulation as a standard diagnostic and rehabilitative tool in the array of instrumentation available to today’s clinician. Electromyography and cardiac pace-making are two of the most outstanding applications in today’s clinical and research environments. Most recent applications also include the use of electrical stimulation of muscle and nerve fibres as a rehabilitative treatment tool for chronic pain or to reduce the effects of paralysis.

3.1: Basic Principles of Neuromuscular Physiology

Therapeutic application of NMES relies on the physiologic principles that govern the excitability of nerve and muscle fibres. The nerve cell, known as the neuron, is the basic unit of the communication networks of the body. Its unique

function is the modification and transmission of information from one region of the brain to another, and from the brain to the body and vice versa. The main structural elements of the neuron are its cell body and its dendrites and axon. Neurons communicate with each other via these structural elements. Dendrites are usually thicker and shorter extensions of the cell body than axons and tend to be highly branched. This feature of the dendritic network is known as the dendritic tree. Dendrites act as “antennae” of the cell as they receive information from other nerve cells and are covered with synapses, specialised areas that form connections to the axons of other cells. Axons, tube-like structures that arise from the cell body extending over distances between micrometers to meters, convey information away from the nerve cell to the synaptic terminal where they connect to other nerve cells, muscles or organs (Bear, Connors & Paradiso, 2006).

In the body, information is conveyed through short-lasting electrical events, known as action potentials. Action potentials are generated by a brief reversal of the relative polarity difference that exists between the intra- and extra-cellular environments across the nerve membrane at rest. This polarity difference is created by the cell membrane, whose biochemical objective it is to monitor and regulate the flow of ions, in particular sodium and potassium ions, between the intra- and extra-cellular space. In the resting state, a high concentration of intra-cellular potassium ions is opposed to an extra-cellular environment with a low concentration of potassium ions. In contrast, the concentration of sodium ions is low within the cell and high outside the cell. This imbalance of ion concentrations generates a relative polarity difference across the cell membrane, with a relative negativity inside the cell. This is called the “resting potential”. Changes in the permeability of the cell membrane alter the degree of polarity difference between the intra-and extra-cellular environments. This process is called “depolarisation” and is characterised by the

influx of sodium ions into the cell. If the cell is depolarised beyond a certain threshold, sodium channels in the cell membrane of the axon open and allow the rapid influx of sodium ions. This influx of positively charged ions reverses the polarity difference by making the intra-cellular environment positively charged for approximately one millisecond. Thereafter, potassium-permeable channels in the cell membrane open and allow the rapid outflow of potassium ions into the extra-cellular space, which re-generates the initial polarity difference. At this stage, however, sodium and potassium ion concentrations are reversed in the intra- and extra-cellular spaces. Special “sodium-potassium pumps” in the cell membrane exchange ions in order to re-establish the ion concentrations of the resting state. During this time, the cell is in a state called “refractory period” during which no depolarisation, that is, generation of action potentials, can occur. Because action potentials are uniform “all-or-nothing” responses to changes in the cellular polarity, the transfer of information is coded primarily by the frequency of action potentials conveyed by the nerve, the number of activated nerve fibres and the number of synaptic connections to other cells (Bear et al., 2006).

In the neuromuscular system, the contraction of muscle fibres is initiated and maintained by action potentials that arrive at the periphery via the motor nerve fibres that innervate the particular muscle. It is these motor nerve fibres that are activated and in turn induce muscle contraction when NMES is administered at adequate intensities (Rattay, Resatz, Lutter, Minassian, Jilge & Dimitrijevic, 2003). A muscle consists of many muscle fibres (myofibres), which in turn consist of many smaller subunits, the myofibrils. Individual motor neurons and the muscle fibres they communicate with are called motor units. Arrival of a single action potential at the neuromuscular junction initiates a cascade of neuro-chemical events that ultimately lead to the contraction of nearby myofibrils. A neurotransmitter, acetylcholine, is

released from vesicles at the axon terminal and diffuses into the near-by muscle tissue, causing depolarisation of the muscle fibre membrane. This initiates a chemically mediated and very brief contraction of the myofibril (twitch) in an “all or none” response. Different levels of muscle force are produced by an orchestrated contraction of various numbers of myofibrils and muscle fibres in unison. If action potentials arrive at the muscle at a sufficiently high frequency, individual twitches will fuse into a continuous contraction, known as tetany. The gradation of muscle force thus depends on the rate of motor nerve firing and the subsequent activation of additional nerve fibres (Baker et al., 1993) (refer to Figure 3, p. 45).

Muscle contraction in response to exogenous electric stimulation responds in very similar ways. Gradation of the contraction depends on the stimulus parameters of the administered electrical current. These parameters, including stimulus intensity, frequency and duration, are explained in more details in the following section.

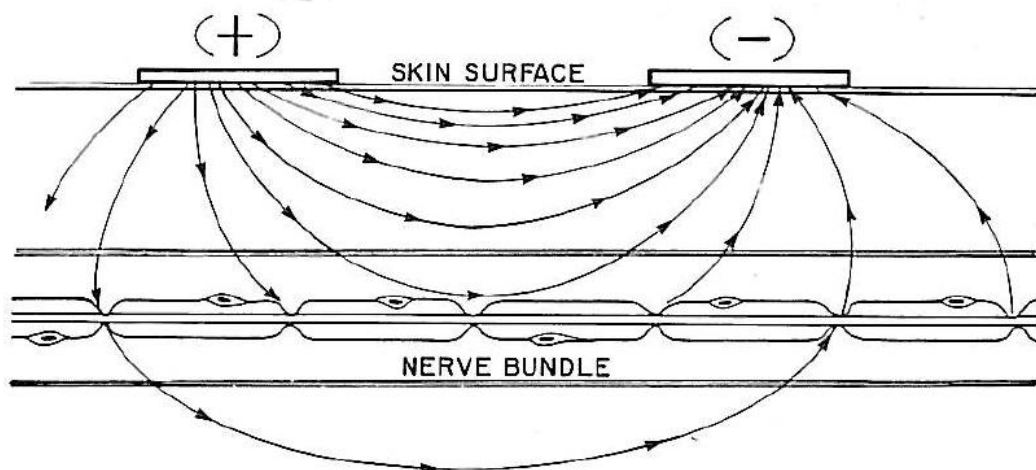
3.2: Basic Principles of Neuromuscular Electrical Stimulation

Using at least two electrodes of different polarity, NMES produces an electrical current flow through movement of ions in the physiologic tissue to which it is applied. In the context of the neuromuscular system, the movement of sodium and potassium ions is of particular interest. By definition, the direction of movement, the current, is oriented from the positively charge electrode, the “anode”, to the negatively charge electrode, the “cathode”. In particular, the anode repels positively charged ions and attracts negatively charged ions. Conversely, the cathode attracts positively charged ions and repels negative charged ions. Therefore, introduction of an electrical stimulus through electrodes positioned over the skin introduces the exchange of electrically charged particles between the electrodes

(Figure 1). In an axon underlying the surface electrodes, excitation mainly occurs under the cathode. This is because it is here that the electric charge of the extra-cellular environment is lowered, that is, made more negative, which decreases the potential difference between the intra- and extra-cellular spaces and brings the axon closer to firing threshold.

Figure 1.

Electric current spread between the anode (+) and the cathode (-) (Baker et al., 1993).



Interestingly, propagation of an action potential generated by exogenous electrical stimulation occurs in both directions, which is a unique phenomenon given that intrinsically generated action potentials propagate in only one direction. This is because segments to both sides of the point of exogenous stimulation of an axon are in a resting, and not a refractory state and can thus be depolarised (Baker et al., 1993). Action potentials that travel proximally toward the cell body will be annihilated there. Action potentials that travel distally will depolarise the muscle fibre and cause it to contract (Peckham & Knutson, 2005).

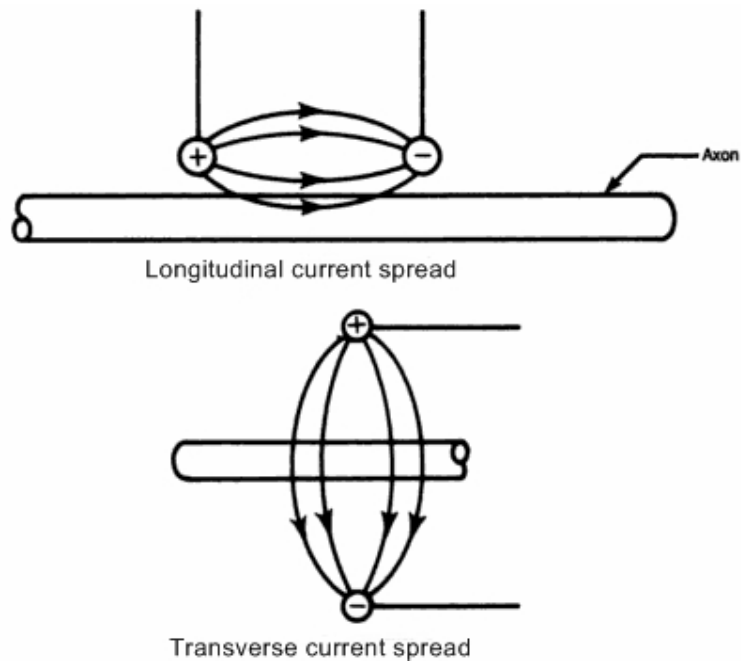
NMES is applied to the tissue as pulses of electrical current. The pulses are characterised by three parameters: amplitude, duration and pulse frequency. Along with other factors such as impedance and electrode size, these parameters influence the effect of NMES on the underlying neural and muscle tissue. Impedance describes the resistance that any given medium opposes to the flow of electrical current. In particular, the amount of current flow is inversely related to the impedance of the medium it flows through. Ohm's law describes this relationship as:

$$V = IR$$

where V is the voltage output of a stimulator, I the electric current and R the resistance opposed to the current by the medium through which it flows. The human skin has the highest resistance of the tissues of the human body, whereas muscle tissue generally shows good conductivity (Shribner, 1975). It is noteworthy that nerve fibres are more readily depolarised when the electrical current runs in the direction of the nerve fibre as opposed to when it runs across it. This is because the relative difference of the electric charge at two points along the axon is greater when current flows longitudinally to the nerve fibre, as opposed to when it transverses it (Reilly, Antoni, Chilbert, Skuggevig & Sweeney, 1992) (Figure 2).

Figure 2.

Current spread across an axon. Nerve fibres are more readily depolarised by longitudinal current spread compared to transverse current spread as the relative polarity difference at two points along the axon is greater for longitudinal current spread (Reilly et al., 1992).



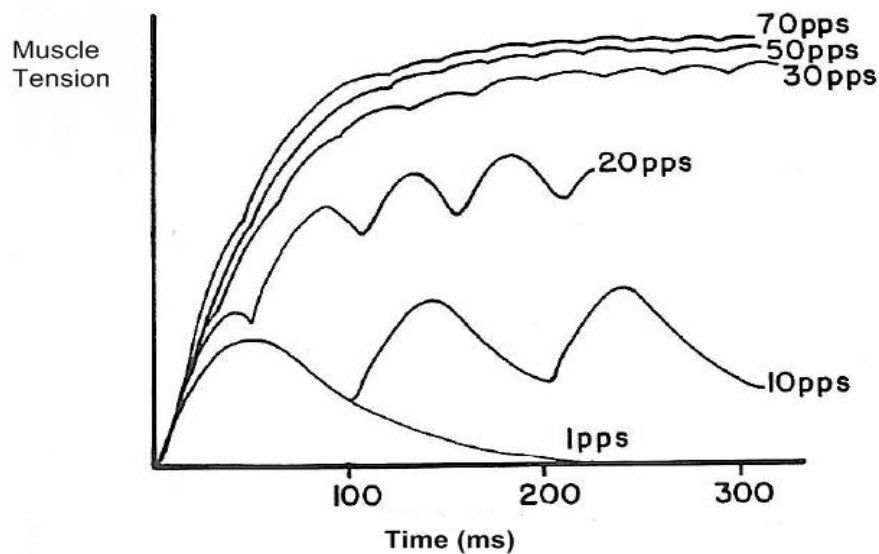
Additionally, the size and orientation of the stimulating electrodes is related to the degree of impedance opposed to the flow of the electrical current. In general, the further the electrodes are apart, the deeper the stimulating current penetrates the underlying tissue. Current flowing between two electrodes that are located close together may thus only penetrate the skin and subcutaneous lipid layers. Electrode size influences the degree of current density, a quantitative measure of current flow per cross-sectional area. Larger electrodes distribute current flow over a larger area, thus decreasing current density, whereas smaller electrodes concentrate current flow to a smaller area, yielding higher current density.

Of principle importance are further the NMES stimulus parameters, in particular pulse repetition rate (frequency), stimulus amplitude (stimulation intensity) and pulse duration, as they greatly influence the strength of the induced muscle contraction.

The stimulation frequency influences the quality of the resulting contraction (Figure 3). At low stimulation frequencies, muscle fibres produce a series of muscle twitches. At higher stimulation frequencies, these twitches fuse into a smooth contraction. The threshold frequency for eliciting a smooth muscle contraction is also referred to as the *fusion frequency* and the cumulative effect of repetitive stimulation is known as *temporal summation* (Peckham & Knutson, 2005). Based on these phenomena, higher frequencies produce stronger contractions.

Figure 3.

Muscle contraction produced by various NMES stimulation frequencies. Note that higher frequencies (pulses per second, or pps) induce tetanic muscle contraction (Baker et al., 1993).



The amplitude of the electrical current also influences the strength of the induced contraction, by recruiting an increasing number of motor units with increasing stimulus amplitudes. This relationship is also known as *spatial summation* (Peckham & Knutson, 2005). In the neuromuscular system, the largest and closest nerve fibres underlying the stimulating electrodes are recruited first. With increasing current intensity, the induced electric field increases proportionately, subsequently depolarising additional smaller fibres close to the electrode and larger fibres further away from the electrode. A similar relationship exists with the duration of the pulse, where a longer-lasting pulse excites more nerve fibres than a pulse of shorter duration. Therefore, stimulus intensity and duration determine which nerve fibres are activated preferentially.

In this context it is noteworthy that exogenously triggered muscle contraction is inherently more fatiguing and metabolically more demanding than muscle contraction in response to natural innervation. This is largely because endogenous recruitment of nerve (and subsequently muscle) fibres is asynchronous, resulting in varying recruitment of muscle fibres at different times and rates during the contraction. Neuromuscular electrical stimulation excites the same nerve fibres repeatedly during the course of the stimulation. Further, the number of activated muscle fibres is smaller during NMES which means that a smaller number of fibres has to fire at a higher rate in order to achieve the same tetanic contraction as would occur during natural innervation (Holcomb, 2006). This inadvertently leads to increased muscle fatigue due to increased neurotransmitter release and is directly related to the strength of the induced muscle contraction (Requena, Padial & Gonzalez-Badillo, 2005). While it is possible to electrically stimulate the muscle itself, the threshold for producing an action potential in a muscle fibre directly is 100 to 1,000 times higher than the threshold for nerve fibre depolarisation (Mortimer,

1981). Due to the relatively low currents produced by clinical stimulators, these systems are limited to stimulating the motor nerves exposed to the electrical current flow. As a rehabilitative approach, the application of NMES is thus limited to patients with intact lower motor neurons, excluding patients with polio, amyotrophic lateral sclerosis (ALS) and peripheral nerve injuries (Peckham & Knutson, 2005).

3.3: Sensory Versus Motor Stimulation

The neural systems that are being stimulated depend to a large degree on the choice of stimulation parameters. Of particular importance in this context is the parameter of stimulus amplitude, as it is the intensity of the electric current that determines the size of the electric field and thus the depth of current spread between the two electrodes (Peckham & Knutson, 2005). In general, both afferent sensory and efferent motor nerve fibres will be subjected to the electrical current induced during NMES. However, due to their closer proximity to the surface electrodes, cutaneous sensory fibres will always be stimulated before and at lower intensities than the motor nerve fibres located deeper in the tissue. Thus, isolated sensory stimulation can be achieved without inducing muscle contraction if NMES intensities are adequately low. This modality has, for example, been used for functional recovery of upper limbs after stroke (Peurala, Pitkaenen, Sivenius & Tarkka, 2002; Wu, Seo & Cohen, 2006). In contrast, isolated motor stimulation cannot be achieved with surface NMES, because (a) cutaneous sensory fibres will always be activated concomitantly and (b) sensory afferents from the contracting muscle will provide additional sensory input about the contractile state of the muscle.

The type and intensity of stimulation which are optimal for inducing lasting changes in the sensorimotor system is debated. On a theoretical basis, it may be

argued that if changes in measures of muscle strength are desired, then stimulation levels should be adequately high to induce muscle contraction. Indirect evidence for this hypothesis can be referred from the study by Fraser et al. (2002) who documented that only high intensity stimulation (75% of maximal tolerated intensity) induced lasting changes in the excitability of the pharyngeal motor cortex. Further, neurophysiological studies in animals (Nudo, Wise, SiFuentes & Milliken, 1996) and humans (Asanuma & Keller, 1991) have demonstrated that repetitive movement and its associated afferent inputs improve motor function. It can thus be argued that NMES at intensities that induce muscle contractions (as well as afferent feedback) would be superior to purely sensory NMES at low stimulation intensities. A similar view is shared by Glinsky and Harvey (2007) who comment in a review on the efficacy of electrical stimulation to increase muscle strength, that “although some researchers believe that this... (sensory) form of electrical stimulation increases voluntary strength, most do not” (Glinsky & Harvey, 2007, p. 176).

For the application of NMES in swallowing rehabilitation, the differentiation between purely sensory and combined sensorimotor stimulation is of particular interest. Swallowing impairment may present secondary to a variety of underlying causes, including (a) muscle weakness, associated with impaired oral bolus control, premature spillage and inadequate pharyngeal clearance, (b) sensory deficits, associated with delayed onset of pharyngeal swallow and reduced sensitivity to pharyngeal residue or (c) and combination of both. The question arises which particular impairment can be best improved with NMES. One would presume that if muscle weakness were an underlying issue, then NMES would need to be of adequate intensity to elicit muscle contraction. High intensity stimulation is common practice in most clinical applications, however, depending on the site of application, may induce the unwanted side effect of hyoid decent during stimulation (see below

review of Humbert et al., 2006 and Ludlow et al., 2007). Alternatively, if sensory deficits are the main cause for the swallowing impairment, then isolated sensory stimulation may be sufficient to improve swallowing function. However, it has not been directly evaluated whether the commonly targeted, external muscles, such as the submental or laryngeal musculature, are the appropriate sites for sensory stimulation. Increased sensory input would be expected to be of particular importance for triggering the pharyngeal phase of swallowing, and thus might be best applied to the posterior oral cavity or upper pharyngeal areas. Indeed, non-event-related NMES at relatively high intensities (75% of the individual pain threshold), administered to the faucial pillars (Power et al., 2004) or pharyngeal musculature (Fraser et al., 2002) has been shown to both positively and negatively affect swallowing function in healthy volunteers. The choice of stimulation site and stimulation parameters should therefore be an important factor in the pre-treatment planning for NMES intervention in swallowing rehabilitation.

In summary, NMES induces a number of electrochemical changes in the neural and muscular tissue by changing the ionic composition of the neural or muscular cell membrane. If of sufficient intensity, this leads to the generation of action potentials with subsequent stimulation of sensory networks and muscle contraction. A number of variables may influence the effects of NMES on the neuromuscular system and this may also have consequent implications for plastic changes in the central nervous systems. In general, the processes of action potential generation and transmission evoked by NMES rely on the same processes of neurochemistry as naturally occurring excitation. However, the exogenously introduced excitation by NMES is metabolically more demanding because it cannot mimic the natural, energy-conserving innervation pattern produced by internal, natural neural excitation.

3.4: Application of NMES in Physical Rehabilitation Medicine

3.4.1: Effect of NMES on biomechanical function and peripheral motor recovery. The literature in physical medicine and rehabilitation has documented a variety of applications for electrical stimulation, including muscle strengthening and improved motor control, prevention of disuse atrophy or pain control (Kit-Lan, 1992). A large number of studies have investigated the effects of NMES on a variety of outcome measures related to these treatment goals. The literature review provided in this subchapter focuses on NMES treatment effects on muscle strengthening and motor control, as these factors would be expected to be primarily relevant for the rehabilitation of swallowing function. It provides an overview of the research undertaken in this area of rehabilitation medicine to elucidate current issues regarding this treatment approach, including (a) whether NMES provided in a functional context (event-related NMES) produces superior treatment effects compared to non-event-related NMES when the target muscle is at rest, (b) whether improvements in isolated outcome measures relate to improvements in functional use and (c) whether the observed effects immediately post treatment can be sustained over time after conclusion of treatment.

In a meta-analysis of four randomised controlled trials assessing the efficacy of event-related NMES in rehabilitating hemiparesis post-stroke, Glanz et al. (1996) concluded that the data reviewed in their analysis provided evidence for the favourability of NMES treatment. All of the included studies investigated the effects of event-related NMES on muscle force produced by wrist extension, knee extension or ankle dorsiflexion. All studies reported some gains in muscle force production after event-related NMES, with two studies reporting statistical significance. The mean effect size across the four studies was $d = 0.63$. Only one study provided a sham stimulation treatment, the other three studies investigated effects after event-

related NMES intervention with no comparison to other treatments. In summary, this meta-analysis documented beneficial gains in muscle force recovery post-stroke after event-related NMES. However, this analysis is limited in that only a small number of studies were included, which did not provide enough data to compare the effects of event-related NMES to other treatment approaches or to investigate potential benefits on functional outcome measures. Nevertheless, the reviewed studies provide limited evidence for the usefulness of this treatment approach.

Bolton et al. (2004) reviewed the effect sizes reported by five studies evaluating the effects of event-related NMES treatment on arm and hand function in post-stroke patients. A total of 47 patients (84% in chronic, 16% in acute and subacute phases) and 39 control patients were represented across the reviewed studies. Four of the studies compared functional outcomes after event-related NMES intervention to those observed after usual stroke therapy, including voluntary movement attempts, and Bobath or occupational therapy, whereas one study compared outcome to no treatment at all. Overall, a mean effect size of $d = 0.82$ in favour of event-related NMES treatment was documented. In summary, the authors concluded that event-related NMES produces improved function of the arm and hand and commented that some degree of voluntary muscle control is crucial for the genesis of positive effects through electrical stimulation treatment. This, however, was an observation that was not directly assessed in this meta-analysis. In support of the findings reported by Glanz et al. (1996) who only investigated effects on muscle strength, Bolton et al. documented beneficial effects of event-related NMES on functional measures of hand and arm use. Interpretation of the result warrants caution, as this meta-analysis is limited by the small number of studies included in the effect size calculations.

De Kroon, Ijzerman, Chae, Lankhorst & Zilvold (2005) evaluated the relationship between NMES parameters and clinical outcome measures related to motor control of the upper extremities after stroke. Nineteen clinical investigations were included in this meta-analysis, representing 22 patient groups and a total of 578 patients in acute (four studies), subacute (two studies) and chronic stages (10 studies); three studies included patients from several stages. Statistical analyses employed univariate logistic regression analysis for continuous variables or chi-square analysis for categorical variables. Treatment parameters investigated included stimulus frequency, amplitude, pulse width and treatment duration, as well as task context during which NMES was provided. No statistically significant relationship was found between treatment duration or stimulus frequency, and treatment effects, respectively. The authors hypothesise that because all studies had employed NMES at intensities that induced visually observable muscle contractions, “muscle contraction is crucial in the effect of ES (electrical stimulation), rather than stimulus parameters” (DeKroon et al., 2005, p. 72). No statistical analyses were undertaken for amplitude data because the included studies did not provide sufficient information of absolute values, rather reporting that amplitudes were individually adjusted based on degree of muscle contraction. Measures of pulse width were similar across studies (200 or 300 μ s) and thus would not have had differential effects on treatment outcomes. The only statistically significant relationship was identified for the task context during which NMES was administered. Event-related NMES was statistically more likely (2.7 times) to induce a positive treatment effect than non-event-related NMES. Of the studies employing event-related NMES, 88.9% produced positive outcomes, as opposed to only 33.3% of studies employing non-event-related NMES. In explanation of the overall positive effects of both types of NMES treatment, the authors hypothesised that the stimulus intensity employed

in most studies was adequately high to produce muscle contraction. This likely produced afferent feedback from muscles and joints, which in turn increased excitability in the cortex. In regards to the superiority of event-related NMES, the authors concluded that event-related NMES likely produced beneficial outcomes more often than non-event-related NMES, because of the cognitive involvement during this type of NMES treatment. This, however, remains speculative, as none of the studies have directly compared the effects of event- and non-event-related NMES.

Bax et al. (2005) undertook a meta-analysis of 35 studies evaluating the effects of NMES on measures of strength of the quadriceps femoris muscle, which targets knee extension. For the unimpaired muscle, meta-analysis of 12 studies (235 research participants) evaluating non-event-related NMES versus no exercise revealed that non-event-related NMES produced superior effects on measures of muscle strength. Only two studies compared the effects of event-related NMES compared to no exercise. Both studies reported results in favour of event-related NMES, however differences reached statistical significance in only one study. Meta-analysis of eight studies (155 research participants) investigating the effects of non-event-related NMES versus volitional exercise did not reveal significant differences between the two approaches. For the impaired quadriceps femoris muscle, most of the included studies favoured the use of non-event-related NMES during (two of three studies) and after an immobilisation period (five of seven studies) by preventing strength loss in the immobilised leg, over no exercise. When comparing the effects of non-event-related NMES to those of volitional exercise, only one of five trials produced results in favour of NMES. The authors conclude that NMES has the potential to facilitate quadriceps femoris strength and may be of particular value during an immobilisation period. However, for the unimpaired

muscle, volitional exercises may be more than or at least as effective as NMES. In regards to the question whether event-related or non-event-related NMES produced superior results, the authors state that “the presence of a volitional component in the NMES-induced contraction appears relevant for the efficacy of NMES” (Bax et al., 2005, p. 210). This statement, however, is not based on a direct comparison of the two types of NMES.

Sheffler and Chae (2007) provided a narrative review of studies investigating the effectiveness of NMES for motor relearning in the stroke population. Three types of NMES were reviewed independently: cyclic (non-event-related) and emg-triggered (event-related) NMES and electrical stimulation used in form of neuroprotheses. For upper limb applications, four randomised studies reported improved outcomes in measures of motor impairment after cyclic NMES. Effects were reported to be more significant and longer lasting in acute phase patients or those that initially presented with less severe deficits. Six studies employing event-related NMES were reviewed and all yielded improved measures of impairment post treatment. One study reported that the positive treatment effect persisted at a 9 months follow up and two studies also reported improved functional outcomes. Three studies documented changes in neurophysiological measures, as assessed with fMRI. For all reviewed studies, the authors critique a variety of methodological limitations that prevent definite conclusions about the effectiveness of these approaches, including lack of rater blinding, follow-up evaluations, detailed information about treatment paradigms and outcome measurement, and small sample sizes. To evaluate the effects of neuroprotheses, the authors reviewed two studies, one including patients in the chronic phase post-stroke and one including patients in the acute phase. For both studies, significant improvements of motor impairment and hand function were reported.

While this review reports a potential use for NMES application in neurorehabilitation overall, the interpretation of the reviewed data is severely limited by the narrative nature of this review. Virtually no data in regards to selection criteria, treatment paradigms, outcome measurements and statistical analyses are reported. No clear evidence can thus be gained in regards to the abovementioned questions as to which type of NMES application is favourable, whether any type improves functional measures and whether treatment effects are long lasting.

Glinsky, Harvey and Van Es (2007) evaluated the efficacy of NMES interventions for increasing muscle strength in several neurological disorders (spina bifida, cerebral palsy, peripheral nerve lesion, multiple sclerosis, spinal cord injury and stroke). Except for the stroke category, which included 11 studies all other categories included only one study and are therefore not further reviewed here. In the stroke population, electrical stimulation paired with conventional therapy was compared to conventional therapy alone in seven studies. Due to high heterogeneity, probably related to inclusion of different muscle groups in the analysis, no meta-analysis was undertaken. Two of these studies compared the two treatment approaches for the wrist extensor muscles and favoured NMES assisted therapy over conventional therapy. Similar results were found for the ankle dorsiflexor muscles, for which two studies favoured NMES assisted therapy over conventional therapy. For the quadriceps muscles, two studies indicated increased measures of strength, however, because of the very large confidence intervals the certainty in the estimation of this effect is low. The authors conclude that there is, therefore, no compelling evidence for the efficacy of NMES assisted therapy for this muscle group. The seventh study measured muscle strength on a six-point rating scale, rather than evaluating objective measures of torque. While the relative increase in strength was reported to be 66% for the hand extensor and 64% for the ankle

extensors, the large confidence intervals prohibited firm conclusions about the superiority of either treatment approach to be drawn.

Two further studies were reviewed that compared NMES intervention with sham stimulation. One study compared non-event-related NMES paired with conventional therapy to sham stimulation paired with conventional therapy. For the ankle dorsiflexor muscles, NMES assisted conventional therapy proved to be superior to conventional therapy paired with sham stimulation. The second study compared event-related NMES with sham stimulation on finger extensor strength. For measures of strength, no differences were found between the two treatment approaches. However, functional measures of finger use increased only after event-related NMES and were accompanied with changes in cortical motor activity (Kimberley, Scott, Auerbach, Dorsey, Lojovich & Carey, 2004, reviewed below).

Finally, two studies compared the effects of NMES paired with functional task performance to functional task performance alone. In one study, measures of range of motion, indicative of contractile strength, improved more after NMES assisted grasping training than after grasping training alone and persisted at a 6 months follow up. For the other study, which investigated treatment effects on measures of gait, insufficient data were reported to calculate mean differences and thus to draw any conclusions.

In summary, the authors conclude that across the reviewed studies, no consistent evidence exists for the superiority of NMES-assisted therapies for the recovery of strength after stroke, but that it may be better than no treatment at all. This last hypothesis, however, was not directly investigated in this review. Further, the authors comment that (a) while some studies have indicated increased strength after NMES-assisted therapy, no direct relationship to consequent increases in limb function was proven and (b) no clear evidence could be found for an additional

benefit that may be related to NMES triggered by a functional task. This review is limited in that no statistical meta-analyses were performed on the reviewed data. Narrative comparisons were based on confidence intervals, and only where available. In agreement with most other publications reviewed in this subchapter, this review documented substantial differences between research paradigms, outcome measurement and analyses employed across the reviewed studies. This may in part be due to the broadly defined inclusion criteria, which permitted evaluation of any muscle or muscle group and a variety of underlying neurological disorders.

Meilink, Hemmen, Seelen and Kwakkel (2008) used narrower inclusion criteria to investigate the effects of event-related NMES on functional measures of the wrist and fingers extensors compared to conventional therapy. Eight studies (representing 157 patients in the acute and chronic phases post stroke) were included in the literature review. Functional measures of interest were reaction time, sustained contraction, dexterity (Box and Block Manipulation Test), synergism measures (Fugl-Meyer Motor Assessment Scale) and manual dexterity (Action Research Arm Test). For all outcome measures, pooled effect sizes were non-significant, indicating that event-related NMES therapy is not superior to conventional therapy. This finding is in direct contrast to the meta-analysis undertaken by Bolton et al. (2004) who reported significant benefits after event-related NMES. The authors commented that this might be due to the relatively small sample sizes included in their analyses, and methodological limitations of the reviewed studies. For example, “conventional therapy” in two studies included non-event-related NMES and in two different studies, conventional therapy was provided two to three times more frequently than event-related NMES intervention. Low statistical power also limited the validity of the reviewed findings. Further, the authors commented that the non-significant differences between treatment approaches may be related to the fact that patients in

the chronic or subacute phases post stroke were investigated in the reviewed studies. Based on previous studies, they suggested that initiation of event-related NMES in the acute phase post stroke provides greater benefits from this treatment. One may argue, though, that benefits from any type of rehabilitative treatment are not easily quantifiable in this post stroke stage as spontaneous recovery may account in part for any observed improvements. In summary, the findings of this study again reflect the issue that no clear evidence exists in regards to (a) the effects of NMES on isolated or functional measures and (b) whether event-related NMES and non-event-related NMES differ significantly in their effectiveness. It further raises another important question, which is also relevant for the use of NMES in swallowing rehabilitation: when is the best time to commence treatment?

In conclusion, the reviewed meta-analyses and literature reviews provide no clear evidence for the efficacy of NMES in neurorehabilitation after stroke. In relation to the questions posed above, (a) many authors have commented that a volitional component during exercise, as present during event-related NMES, is crucial for the efficacy of this treatment in the corticospinal nervous system. Non-event-related NMES may in some circumstances contribute to the recovery of or increase in contractile muscle strength, but it is unclear whether this translates to improvement of functional ability. This requires further investigation. A limited number of studies have indicated that improvements in isolated measures, in particular of muscle strength, relate to improved limb function (b). However, most studies have not directly investigated this relationship. Even fewer data are available in regards to the question whether (c) observed treatment effects persisted after conclusion of treatment. Therefore, no strong conclusions can be drawn from the presented data to answer these questions.

Overall, the comparison and interpretation of the many research studies reviewed in these meta-publications is limited in several ways. In particular, a vast variety of muscles groups have been investigated in many participant groups (both healthy and impaired), many different treatment paradigms and statistical analyses have been employed, and reporting methods are also vary considerable. Thus, direct comparisons are difficult to perform and virtually all meta-publications have listed the above issues as limitations to their interpretations.

3.4.2: Effects of NMES on cortical mechanisms. Recent research has indicated that NMES may have effects not only on a functional level, but can also induce adaptation on a cortical level. For example, Kimberley et al. (2004) have demonstrated that event-related NMES of the extensor muscles of the hemiplegic forearm of 16 chronic stroke patients facilitated functional use of the hand (grasp and release, isometric fingers extension strength and self-rated motor activity log). This increase in functional use was related to increased activity in cortical sensory areas based on fMRI signal intensity, although the number of activated voxels did not change. The changes documented in the treatment group were not observed in a sham stimulation group. Interestingly, after sham treatment (consisting of a finger extension task) patients in the sham treatment group improved on measures of isometric finger extension strength, but this did not translate into improvement of any other functional hand movements. In agreement with prior studies, the authors hypothesise that “functional hand movements may depend more on orchestrating synergistic control of multiple muscular forces than on sheer strength alone, and the possibility exists that NMES helps to activate neurons that can improve such control” (Kimberly et al., 2004, p. 456).

Similarly, Thompson and Stein (2004) reported that event-related NMES applied to the ankle dorsi-flexors of 10 healthy research participants during walking resulted in greater MEPs elicited by TMS than after walking alone. The authors comment that the combination of locomotor activity and event-related NMES may effectively facilitate beneficial, plastic reorganisation in the central nervous system.

Peurala et al., (2002) investigated the role of non-event-related NMES in functional post-stroke recovery. Fifty-nine patients underwent a conventional 3-week inpatient rehabilitation programme; 51 of these patients additionally received subthreshold sensory NMES twice daily for 20 min, whereas 8 patients received sham NMES treatment. Outcome measures included measures of motor function, paretic limb function, limb skin sensation scores and somatosensory evoked potentials (SEPs). For functional measures, the authors reported improved scores in all outcome measures for the group that received active sensory NMES treatment, but not the sham treatment group. The authors further documented that this functional improvement was accompanied by an improvement in the size and shape of SEPs for the paretic upper and lower limbs. Additionally, SEP components were measurable in some patients that did not display any SEPs pre-treatment. The interpretation of this study is limited as the two treatment groups were of considerably different size and no data in regards to differences of age, gender or impairment level were provided.

Golaszewski, Kremser, Wagner, Felber, Aichner & Dimitrijevic (1999) reported that after 20 min of subthreshold sensory NMES, fMRI signal activity in the primary and secondary motor and somatosensory areas was increased. Six healthy subjects underwent fMRI during finger-to-thumb tapping before and after 20 min of subthreshold, non-event-related NMES of the whole hand provided via mesh-glove stimulation. Increases in blood oxygenation levels in these areas during post-

treatment performance of the motor task were thought to be related to changes in the metabolic demand due to increased neural activity.

In summary, these data indicate that changes in the excitability of sensory and motor cortices occur in response to electrical stimulation of peripheral nerves and muscles. While some studies indicate a relationship between increased cortical activation and measures of functional performance, research is warranted to evaluate this relationship further.

3.4.3: Early hypotheses regarding NMES-induced changes in CNS

function. No clear understanding exists as to why and how exactly changes of corticobulbar or corticospinal excitability occur in response to NMES. The concepts of long-term potentiation (LTP) and depression (LTD) have been discussed as potential origins for altered synaptic plasticity (Fraser et al., 2002; McKay, Brooker, Giacomini, Ridding & Miles, 2002a; Ridding, Brouwer, Miles, Pitcher & Thompson, 2000).

LTP is documented to result from coincident excitation of pre- and post-synaptic elements, which facilitates trans-synaptic chemical transmission (Bliss & Gardner-Mewin, 1973). In contrast, LTD decreases synaptic efficacy and can be induced by low-frequency stimulation (Dudek & Bear, 1992) or mismatched pre- and post-synaptic activation (Markram, Lubke, Frotscher & Sakmann, 1997). Bliss and Lomo (1973) were the first to describe the concept of LTP and LTD in the context of memory acquisition and learning in animals. A body of research is now available that describes LTP and LTD induction in the healthy and impaired human central nervous system following a variety of central and peripheral stimulation applications (Cooke & Bliss 2006). Changes in synaptic efficiency or excitation threshold of the stimulated cells were mentioned as possible causes for the reported

changes in neural excitability. A similar hypothesis was proposed by Sanes and Donoghue (1992) who suggest that inactive or weak synapses may be activated by the altered peripheral stimulation, therefore influencing cortical activity levels. Interestingly, the induction of plastic changes does not seem to occur immediately, but changes evolve over the time course of approximately 60 min. For example, such time courses have been reported for the effects on MEPs after altered peripheral input to the cranial muscles (Hamdy et al., 1998a; Fraser et al., 2002; Power et al., 2004), hand muscles (Stefan, Kunesch, Cohen, Benecke & Classen, 2000; Ridding, Brouwer, Miles, Pitcher & Thompson, 2000) and arm muscles (Ziemann, Corwell & Cohen, 1998). This time course of LTP and LTD induction is thought to relate to depolarisation of the post-synaptic cell in response to repetitive synaptic activation, which releases Mg^{2+} ions from blocking N-methyl-D-aspartate (NMDA) receptor gated ion-channels in the cell membrane. This consequently allows the rapid influx of Ca^{2+} ions into the post-synaptic cell, a process thought to increase or decrease synaptic strength for up to 2 hrs (Thompson, Mattison & Nestor, 1999; Malenka & Nicoll, 1999). However, the precise mechanisms that govern central changes in excitability in response to altered peripheral sensory feedback and the time course of the induction of the changes remain unknown

Of relevance for the induction of plastic changes in response to event-related NMES may also be the concept of interventional paired associative stimulation (IPAS) (Stefan et al., 2000). LTP induction was documented after IPAS, when a peripheral electrical stimulus was administered at an interval of 25ms prior to a magnetic stimulus to the motor cortex. This interval corresponds with the latency of a cortical SEP elicited by peripheral electrical stimulation. Excitability of the hand motor cortex increased after 90 paired stimulations, as determined by increased MEP amplitude recorded from the abductor pollicis brevis muscle in the thumb.

Coincident activation of motor neurons by the ascending sensory stimulus and TMS was thought to be the driving mechanism for the observed increase in cortical excitability. Similar results were reported by Ridding and Taylor (2001) who demonstrated increased MEP amplitude recorded from the first dorsal interosseous muscle after IPAS with an inter-stimulus interval of 25 ms. In contrast, Wolters, Sandbrink, Schlottmann, Kunesch, Stefan, Cohen et al. (2003) demonstrated that mismatching peripheral and cortical stimulation, by shortening inter-stimulus intervals, induced a reduction of cortical excitability. It is possible that similar mechanisms of plasticity underlie the effects reported after event-related NMES as exogenous electrical stimulation of the peripheral musculature coincides with the endogenous cortical activation during muscle contraction.

3.5: Review of Existing Research into the Effects of NMES on Swallowing Function and Neurophysiology².

Since its commercial application in the area of swallowing rehabilitation, the use of NMES has become a hotly debated topic in both the clinical and research communities of dysphagia rehabilitation. While some clinical studies have demonstrated improvements of swallowing function in patients whose progress had plateaued using “conventional” dysphagia rehabilitation approaches (Freed, et al., 2001), others have documented no clinical benefits from this technique or even the potential for harmful side effects (Humbert, et al., 2006). A chronology of the research undertaken in both clinical and research areas is summarised in the following chapter. First, basic research investigating effects on clinical and

² A modified version of the literature review presented in this section has been published by Huckabee and Doeltgen (2007b). It also served as the basis of a position paper adopted by the New Zealand Speech Therapist’s Association (NZSTA) on the use of NMES in swallowing rehabilitation in New Zealand (Huckabee and Doeltgen, 2007a).

biomechanical measures of swallowing is summarised, followed by a review of research specifically investigating the effects of a treatment paradigm called VitalStim™. Lastly, the effects of NMES on neurophysiological measures underlying swallowing are discussed.

3.5.1: Effect of NMES on clinical swallowing function and swallowing biomechanics. Park, O'Neill and Martin (1997) were the first to use electrical stimulation in the context of swallowing rehabilitation. In 4 stroke patients with chronic dysphagia and the physiologic abnormality of “delayed swallowing reflex”, oral electrical stimulation was applied to the posterior soft palate through a custom designed palatal prosthesis. Stimulation intensity was set to the individual's maximum tolerated intensity level and stimulus characteristics were set with a duration of 200 μ sec, repeated at 1 Hz. In this limited sample of four case studies, non-event-related NMES did not facilitate timelier onset of swallowing. However, 2 of the 4 patients enrolled into this study showed improvement in bolus transit time and penetration/aspiration scores after non-event-related NMES treatment. A limitation of this research is the lack of justification in regards to the selection of stimulation parameters, although these were clearly specified. This innovative research suggests, however, that there may be some clinical use of this technique and the authors conclude that further research is warranted to explore the reproducibility of the presented data, include a greater variety of outcome measures and ultimately study treatment protocols in systematic group comparisons.

Subsequent to this initial exploration of non-event-related NMES in swallowing rehabilitation, Freed et al. (2001) investigated the clinical effects of a non-event-related NMES treatment protocol using surface stimulation electrodes applied to the floor-of-mouth and laryngeal areas. One hundred and ten stroke

patients with swallowing disorders at an unspecified time post stroke were investigated for this purpose. Sixty-three of the 99 patients that completed the study were enrolled in a non-event-related NMES treatment group while only 36 patients received thermal tactile stimulation (TS), which was considered a “standard” treatment protocol for swallowing rehabilitation. Patients received a course of 60 min of non-event-related NMES or thermal stimulation treatment sessions, which were administered by the primary investigator daily for inpatients and three times per week for outpatients. Outcome measure was a score of swallowing function, which was assigned to each patient by the principal investigator based on pre- and post-treatment videofluoroscopic swallowing studies (VFSS). Functional scores were based on a non-standardised rating scale, which documented the ability to safely swallow different food consistencies. Treatment continued until patients achieved a swallowing score of 5 out of a maximal 6 points, or until progress plateaued, as determined by the principal investigator. The authors report that 98% of the patients in the non-event-related NMES group improved in functional swallowing scores, whereas only 69% of TS patients improved post-treatment.

The methodological design of the original research undertaken by Freed et al. limits the validity of the results in several ways. The choice of stimulation parameters employed in this protocol lacked justification. Further, the “standard” treatment of thermal-tactile stimulation is a poorly understood technique and its effectiveness has not been sufficiently investigated or supported. Therefore, comparing the effects of a novel treatment approach to this treatment is problematic. The functional rating scale used to assess outcome measures has not previously been validated and the ratings were assigned only by the primary investigator, who also provided the treatment. Importantly, an unspecified number of patients in the non-event-related NMES group concomitantly underwent dilatation of the upper

oesophageal sphincter. This intervention is an accepted treatment in its own right. Specifically, UOS dilatation is performed in order to aid safe pharyngeal bolus passage and therefore may have positively biased swallowing ratings for participants in the stimulation group. These methodological flaws affect the validity of the reported positive results; therefore the documented effects must be interpreted with caution.

Despite these substantive limitations, results of this study and that by Park et al. (1997) suggested potential for the application of NMES in swallowing rehabilitation. Leelamanit et al. (2002) were the first to provide NMES in a swallowing-related, functional context. Twenty-three stroke patients with moderate to severe dysphagia, characterised by reduced laryngeal elevation, and a time post onset ranging from 3 to 12 months, were included in this study. Stimulation was provided through surface electrodes overlying the thyro-hyoid muscles and event-related NMES was triggered from surface EMG activity recorded during swallowing. Stimulus frequency of NMES was set to 60 Hz, with a stimulus intensity of 100 V. Patients attended 3-30 treatment sessions of 4 hrs per day until they demonstrated improved swallowing function. As in the study undertaken by Freed et al. (2001), treatment outcomes were rated by the primary investigator based on a patient's ability to swallow more than 3 ml of water without clinical signs and VFSS evidence of aspiration, adequate oral intake with weight gain, and improved laryngeal elevation. Of the 23 patients, 20 demonstrated clinical improvement, whereas 3 patients had no improvement. Of the 20 patients that demonstrated clinical improvement, 6 patients relapsed on follow-up assessments at two to nine months, but could regain benefits after a subsequent course of treatment. Some flaws in the methodology employed in this study limit the validity of the documented results. No control group receiving sham stimulation was used in this research and

aetiologies and time post onset varied substantially. Further, outcome measures were assessed by the primary investigator and no specific criteria for the assessment of aspiration severity were offered. Additionally, no quantitative data were presented on some of the main outcome measures, such as the degree of laryngeal elevation or UOS opening during swallowing post-treatment.

Changes in laryngeal elevation during swallowing were investigated in a study providing intra-muscular electrical stimulation to three muscles involved in swallowing (Burnett, Mann, Cornell & Ludlow, 2003). Fifteen healthy male participants received trials of single, bilateral and combined electrical stimulation to the mylohyoid, thyrohyoid and geniohyoid. A specific aim of this study was to identify which single muscle or muscle pair would be optimal for assisting laryngeal elevation and subsequent airway protection. Laryngeal elevation and movement velocity were calculated based on superior movement of the thyroid prominence and were quantitatively expressed as percentages of change in thyroid movement during a 2 ml swallow. Unilateral stimulation of the target muscles produced an approximate 30% increase in thyroid elevation and an approximate 50% increase in elevation velocity compared to unstimulated 2 ml swallows. Bilateral stimulation of the mylohyoid or thyrohyoid muscles or a unilateral combination of these muscles produced an approximate 50% of thyroid elevation and an approximate 80% of elevation velocity observed during normal swallowing. These results were found to be promising for the development of patient-operated stimulators with implanted electrodes with the ultimate goal of assisting laryngeal elevation during swallowing. However, due to the disparate methods from prior work, these results do not directly support the immediate clinical application of NMES administered through surface electrodes.

The same group then investigated the effects of self-triggered NMES on electromyographic measures of the mylo- and thyrohyoid muscles in nine healthy adults (Burnett et al., 2005). Each research participant synchronised initiation of self-triggered NMES to normal swallowing behaviour by pressing a trigger with the thumb. Electrical stimulation was delivered through hooked-wire electrodes directly in the muscle and stimulation parameters were set to a frequency of 30 Hz and an intensity that represented the highest comfortable level for each research participant. The objectives of this study were to investigate if participants were able to synchronise triggering of the electrical stimulus to their swallowing accurately and consistently. A further objective was to evaluate if self-triggered NMES would lead to an adaptive reduction of intrinsic activity in the muscles elevating the larynx, because stimulation would be expected to facilitate muscle contraction. Electromyographic measures of mylohyoid and thyrohyoid muscles recorded during baseline swallowing were compared to those recorded during non-stimulated placebo swallowing. Participants were able to accurately and consistently trigger NMES at the onset of thyrohyoid activation. Analysis of peak amplitude, duration and relative timing of EMG activity recorded from either muscle showed no significant differences in these measures between baseline swallows and the non-stimulated placebo swallow. Thus, self-triggered NMES had no effect on the endogenous innervation pattern underlying mylohyoid or thyrohyoid activity. The authors concluded from their findings that the central pattern generators governing the motor control of laryngeal elevation are resistant to adaptation.

Power, Fraser, Hobson, Singh, Tyrell, Nicholson et al. (2006) investigated the effects of 10 min of 0.2 Hz non-event-related NMES or sham stimulation of the faucial pillars 60 min after electrical stimulation. These measures had been identified previously to increase cortical excitability of the corresponding motor area

(Power et al., 2004). Stimulation intensity was set to 75% of the value between sensory and pain threshold and post-treatment outcome measures included laryngeal closure initiation and duration and pharyngeal transit time as observed during VFSS. Measures of aspiration or penetration were assessed using a validated penetration-aspiration scale. Sixteen patients with hemispheric stroke and diagnosed dysphagia participated in this study within two weeks after stroke. In summary, no changes in any of the assessed outcome measures were observed post non-event-related NMES treatment compared to pre treatment baselines within individual subjects. Further, no differences were reported between the outcome measures of the treatment and sham groups. The authors concluded that non-event-related NMES of the musculature underlying the faucial pillars is not an effective treatment for stroke patients suffering from dysphagia.

3.5.2: Emergence of a new modality: VitalStim™. Subsequent to their methodologically limited study, which documented positive clinical outcomes in a group of patients with dysphagia related to different aetiologies, Freed et al. initiated the commercialisation of the VitalStim™ device. This was done without further research into the precise effects and mechanisms of NMES, or stimulation parameters required to achieve beneficial treatment outcomes. To this day, the VitalStim™ device is the only Food and Drug Administration (FDA)-approved electrical stimulation device available for application in swallowing rehabilitation.

After FDA clearance was granted, a number of researchers have investigated the effects of this treatment on swallowing function and biomechanical measures. Suiter et al. (2006) evaluated changes in submental surface EMG activity after 10 hrs of VitalStim™ therapy compared to pre-treatment baselines in 10 healthy volunteers. The researchers employed an AB or BA treatment design where in

condition A no treatment was given and in condition B NMES was provided following the VitalStim™ protocol. This study revealed that seven of eight subjects exhibited no significant increase in myo-electric activity of the submental muscle group post-treatment as assessed during 5ml bolus swallows. Two subjects withdrew from the study due to mild skin irritations after treatment. In order to explain the lack of treatment effects, the authors hypothesised that ineffective stimulus parameters, non-functional muscle innervation patterns, the lack of concomitant swallowing exercises or a ceiling effect of optimal muscle recruitment in healthy individuals may contribute to these findings.

A group of researchers at the National Institutes of Health (NIH) investigated the effects of NMES applied to 10 different surface electrode placements on hyo-laryngeal movement in healthy individuals at rest and during swallowing (Humbert et al., 2006). Electrical stimulation was provided at the maximum tolerated intensity following the protocol described by Freed et al. (2001). Raters were blind to the condition under which swallowing was performed (stimulation or no stimulation). Measures of hyo-laryngeal movement were recorded from VFSS and swallowing safety was established using the NIH-Swallowing Safety Scale. Biomechanical measures included peak elevation of the hyoid and larynx and pharyngeal transit for the swallowing conditions. For the rest conditions, positions of the hyoid and the subglottal air column were compared between stimulated and non-stimulated recordings. In summary, the authors report a significant descent of the hyoid and larynx of up to 10 mm during NMES at rest. During swallowing, significantly reduced peak elevation of both the hyoid and larynx were observed. Additionally, the stimulated swallows were scored as “less safe” compared to non-stimulated swallows.

As demonstrated by the last two studies evaluating healthy research participants, NMES provided in accordance with the treatment protocol advocated by VitalStim™ does not always result in altered swallowing function. Indeed, the study by Humbert et al. (2006) raises concerns about potentially harmful effects of this treatment on swallowing biomechanics.

In order to investigate the effectiveness of the VitalStim™ treatment in a disordered population, the same NIH research group evaluated 11 patients with chronic pharyngeal phase dysphagia of at least 6 months duration (Ludlow et al., 2007). Treatment was provided according to the VitalStim™ treatment protocol. Outcome measures included hyoid movement at rest and during 5 ml or 10 ml bolus swallows, whichever posed the greatest risk for aspiration. Blinded measurement was performed on VFSS recordings at rest and during swallowing during an unstimulated condition, a low-stimulation level condition (just above sensory threshold) and a high-stimulation level condition (near pain threshold). In agreement with the results documented for healthy participants (Humbert et al., 2006), 8 of 10 participants demonstrated hyoid depression of 5 to 10 mm during stimulation of the muscles at rest. However, swallows during the low-stimulation level condition presented a statistically significant reduced risk for aspiration and pooling. In contrast, high-level stimulation had no effect on aspiration or penetration. Interestingly, patients who displayed reduced aspiration had a larger degree of hyoid depression during stimulation at rest. The authors hypothesised that these patients may have experienced a greater resistance to hyo-laryngeal elevation and thus increased their effort to produce sufficient hyo-laryngeal elevation during swallowing. The authors conclude that before NMES is applied to a variety of patient groups, further research is necessary to evaluate which immediate effects can be gained in the presence of specific types of swallowing impairment.

Blumenfeld et al. (2006) compared the effects of VitalStim™ therapy to those achieved by traditional dysphagia therapy. The clinical improvement of 40 consecutive patients who underwent traditional dysphagia therapy (including a combination of therapeutic exercise, diet texture modifications and compensatory manoeuvres) was compared to that of 40 consecutive patients who received NMES treatment according to the VitalStim™ treatment protocol. No data regarding the time post onset were reported and dysphagic symptoms were related to a variety of underlying causes. Both treatments were administered for 30 min per day and patients were assigned a functional swallowing score at the beginning and after conclusion of treatment, based on the non-validated scale used by Freed et al. (2001). In summary, the authors reported that both groups improved significantly, however, patients who received Vitalstim™ treatment improved significantly more than the traditional therapy group. The interpretation of these data is limited by the lack of control for rater bias, especially in light of the fact that the patients in the traditional treatment group were evaluated retrospectively, whereas the patients in the Vitalstim™ treatment group were evaluated prospectively.

Kiger et al. (2006) used a different approach to evaluate the effects of the VitalStim™ treatment protocol compared to traditional swallowing therapy. Twenty-two patients with dysphagia related to different aetiologies and unspecified time post onset were divided into a NMES treatment group and a traditional therapy control group. The NMES treatment group received electrical stimulation according to the VitalStim™ protocol whereas the control group received treatment including exercise programs, swallowing manoeuvres, thermal stimulation and meal observations. Patients underwent pre- and post-treatment VFSS or fiberoptic endoscopic evaluation of swallowing (FEES) and were assigned a swallowing function score based on a non-standardised 7-point ordinal rating scale that

described the patients' oral and pharyngeal swallowing function and their ability to swallow different food consistencies. In the oral phase, patients in the traditional treatment group improved significantly more than patients in the VitalStim™ group. A similar trend was also observed for the pharyngeal phase; however, the difference in pre-to-post-treatment change scores did not reach significance. Further, no differences in change scores were found for diet consistency and oral intake measures between the two groups.

Shaw et al. (2007) undertook a retrospective analysis of 18 patients presenting at an unspecified time post onset with a heterogeneous variety of underlying causes for their dysphagic symptoms, including cerebrovascular accident, vagal nerve neuropathy, amyotrophic lateral sclerosis, viral encephalography and Parkinson's disease. Pre-treatment evaluation of swallowing function included standard modified barium swallow (16 patients) or FEES (2 patients) and patients were assigned scores for the degree of laryngeal elevation, presence of penetration or aspiration and severity of residue. Scores were assigned based on a non-validated rating scale. Further, scores were given for diet intake, swallow delay and overall severity. Data were analysed for the entire group first and then for two subgroups of patients with less severe and severe symptoms. Fifty percent of all patients improved in their overall dysphagia scores. Two out of 5 patients who were initially unable to consume food and drink by mouth improved to small amounts of thick liquids post-treatment. None of the patients in the severe dysphagia group were able to discontinue enteral feeding. Most improvement was reported for the group of seven patients who, pre-treatment, were able to consume small amounts of food and drink orally but were predominantly fed enterally. Six of these patients resumed to oral feeding and discontinued tube feedings. Telephone surveys were undertaken to investigate long-term effects of the treatment on oral

intake status and patient satisfaction. Although response rates were too low to perform statistical analyses, the authors report anecdotally that most patients perceived sustained improvement of their swallowing and all but 1 patient reported that they received some benefit from this treatment. The authors concluded that “VitalStim™ therapy seems to help those with mild to moderate dysphagia” (Shaw et al., 2007, p. 36). Patients with more severe symptoms however, did not gain independence from enteral feeding. No specific evaluation of the effects of aetiology as a contributor to recovery was undertaken. This, along with spontaneous recovery in acute patients, may have a substantial influence on outcome measures.

A case study on a patient with opercular syndrome who received VitalStim™ treatment was reported by Baijens, Speyer, Roodenburg and Manni (2008). Opercular syndrome is characterised by bilateral loss of voluntary facial, pharyngeal, lingual and masticatory movements with exception of reflexive and automatic movements and in this 76-year old male was diagnosed post left hemispheric infarction. Initial dysphagia therapy proved unsuccessful and the patient was fed enterally. VitalStim™ therapy was commenced 1 year post onset and the patient received 1 hr stimulation sessions, on five consecutive days a week for five months. VitalStim™ therapy was provided in conjunction with functional dysphagia treatment provided by the therapist. Post-treatment outcome assessment was performed by the treating therapist using an oral motor function test and a functional oral intake rating scale. In summary, no considerable improvement of voluntary muscle control was observed post-therapy and only minor movements of the lips were documented as imitative tasks in response to demonstration by the therapist. A reported improvement on a functional intake scale from nil by mouth to oral feeding is therefore rather surprising and may be related to a number of causes. It is impossible to determine whether the VitalStim™ treatment, the functional therapy

accompanying this treatment, a combination of both treatments or improved confidence of the treating therapist contributed to a higher post-treatment scoring.

Carnaby-Mann and Crary (2008) investigated the effects of a standardised protocol of swallowing exercises in conjunction with Vitalstim™ treatment in six patients with pharyngeal phase dysphagia, at least six months post onset. Based on clinical and instrumental assessment, outcome measures were recorded pre- and post-treatment and 6 months after completion of the therapy protocol. Treatment included 15 sessions of Vitalstim™ therapy, during which swallowing trials were performed by the patient. Although swallows were performed during NMES, this treatment cannot be considered event-related, as initiation of NMES was not related to movement onset, but was provided continuously independent of the swallowing tasks performed. Non-event-related NMES was, however, accompanied by volitional swallowing trials. Patients were instructed to swallow “hard and fast” after placing and holding a bolus in their mouth. Bolus types and volumes were chosen based on the patient’s ability, and increased during treatment. Post-treatment, blinded ratings documented significant increases in swallowing ability, functional oral intake (as rated on scales published earlier by the investigators), weight gain and patient perception of swallowing ability. Hyoid and laryngeal excursion, specific targets of NMES treatment as performed in this study, were reported to change differentially post-treatment depending on bolus volume and consistency. For some boluses (5 ml liquid bolus) hyo-laryngeal elevation decreased, whereas it increased for nectar thick liquids. However, no statistical values for these comparisons were documented. In summary, the authors conclude that “significant improvements in clinical and swallowing function” (Carnaby-Mann & Crary, 2008, p. 286) were achieved, which were sustained in 80% of patients (4 of 5 patients) at a 6-months follow up assessment. This study received funding from a research grant

by the Chattanooga Group, Hixson, Tennessee, the company that exclusively markets the VitalStim™ stimulation device. Of interest is the observation that the improvements in functional swallowing measures in this study are quite similar to results documented in 45 patients with pharyngeal dysphagia receiving biofeedback-assisted exercise, reported by the same authors (Crary, Carnaby (Mann), Groher & Helseth, 2004). The question arises whether NMES-assisted dysphagia therapy is superior to other treatment approaches utilising less invasive intervention approaches. Initial indication that this may be the case was provided by the study undertaken by Freed et al. (2001), however the interpretation of these results are limited by methodological flaws. Further support for the superiority of NMES-assisted dysphagia therapy over traditional dysphagia therapy can be gleaned from the study by Blumenfeld et al. (2006), who also reported greater benefits from the NMES-assisted approach. In contrast, Kiger et al. (2006) found no significant differences in the efficacy of both treatment approaches.

To explore this question further, Bülow et al. (2008) compared the effects of VitalStim™ therapy to traditional dysphagia therapy in an international clinical trial. Twenty-five patients, at least 3 months post-stroke, were randomly assigned to two treatment groups. Twelve patients received NMES treatment according to the VitalStim™ protocol, and 13 patients received traditional dysphagia therapy. All patients received 15 1-hr therapy sessions. Outcome measures included opening of the upper oesophageal sphincter (UOS), pharyngeal residue, aspiration/penetration (all observed on VFSS), oral motor function scores, nutritional status, and self-evaluation of swallowing performance. This study documented significantly increased oral motor scores, improved nutritional status and significant positive effects on the self-evaluation of patients after both types of intervention. Interestingly, post-treatment changes were not significantly different between the

two treatments. No changes were observed in VFSS measures. Importantly, the subjectively perceived improvement reported by patients post-treatment did not correlate with objective measures on VFSS. In fact, 2 patients in the NMES treatment group were treated for severe aspiration pneumonia 2 months after treatment because they felt they had improved, when in fact, they had not and did not adhere to the recommended diet modifications.

In summary, review of the available literature investigating the effects of NMES and the VitalstimTM treatment protocol on measures of swallowing function and oropharyngeal biomechanics provides no clear evidence as to whether the application of electrical current as a rehabilitative tool for swallowing impairment is a useful approach. The diversity of research and treatment paradigms employed makes direct comparison of results impossible. Interpretation of some studies is further limited by methodological flaws, in particular the failure to account for spontaneous recovery in patients in acute stages post onset. No studies have identified (1) the exact mechanisms that underlie the reported post-treatment changes, (2) which patient populations would benefit most from NMES intervention and (3) whether NMES produces superior treatment outcomes than currently existing approaches. Further, it appears that no clear, evidence-based guidelines exist in regards to the treatment parameters that are to be used when providing NMES to human patients and research participants. To address the latter, basic research has emerged that evaluated the effects of a variety of NMES stimulus parameters on swallowing biomechanics and neurophysiological measures.

3.5.3: Effects of NMES on swallowing-related neurophysiological data. A

research group in Manchester, UK was the first to investigate the effects of electrical stimulation of the pharynx and oesophagus on corticobulbar excitability. In their

first investigation, Hamdy et al. (1998a) evaluated the effects of single and short trains of electrical stimuli on MEPs elicited over the corresponding motor cortices. In seven healthy volunteers, single electrical stimulation pulses administered at intensities just above sensory threshold had no effects on cortically evoked responses. Trains of 25 stimuli administered at intensities just above sensory threshold and at varying stimulus frequencies, induced a shortening of MEP onset latencies at both the pharynx and the oesophagus immediately (100 ms) after stimulation. However, the pharyngeal and oesophageal musculature responded differentially to electrical stimulation. At high frequency (5 Hz and 10 Hz), onset latencies decreased in the pharynx and the oesophagus, whereas at low frequencies (0.2 Hz and 0.5 Hz) only oesophageal onset latencies decreased. No effects on MEP amplitudes were found in response to electrical stimulation of either musculature. In explanation of this discrepancy, the authors hypothesised that electrical stimuli at very short intervals may have increased the excitability of brainstem motor neurons (and hence enhanced corticobulbar transmission) but inhibited cortical motor neurons (and hence did not alter MEP amplitudes). Supporting evidence was found in animal studies, which documented inhibition in “cortical swallowing neurons” (p.865) in response to electrical stimulation (Sumi, 1969). In humans, repetitive stimulation of the vagus nerve was found to decrease epileptiform seizures, hence inferring a reduction in cortical (over-) excitability (Rutecki, 1990). Hamdy et al. (1998a) concluded that “it is possible that cortical inhibition may ensure that once brainstem CPG is activated, cortical discharge is suppressed, so that reflex swallowing can occur without interruption by other volitional commands to swallowing musculature” (Hamdy et al., 1998a, p.865).

The same group then systematically investigated the effects of a variety of NMES treatment paradigms on central mechanisms underlying corticobulbar motor

control. These researchers evaluated the effects of non-event-related NMES applied to the muscles underlying the pharynx (Fraser et al., 2002) and the faucial pillars (Power et al., 2004) on MEPs of these muscles in healthy research participants. Fraser et al. (2002) documented that changes in MEP amplitude were directly related to the frequency of electrical stimulation. One frequency (5 Hz) proved optimal for increasing pharyngeal MEP amplitude³, whereas other frequencies (20 Hz and 40 Hz) reduced corticobulbar excitability. Similar results were documented by Power et al. (2004), who also reported stimulation frequencies that increased (0.2 Hz) or decreased (5 Hz) MEP amplitude recorded from the faucial pillars. The corticobulbar inhibition after 5 Hz non-event-related NMES of the faucial pillars reported by Power et al. (2004) correlated with radiographically documented evidence of significantly increased swallowing response time in normal research participants, thus suggesting an adverse functional effect.

Fraser et al. (2002) documented that the excitatory effects observed in healthy research participants could also be induced in individuals with dysphagia and that an increase in pharyngeal corticobulbar excitability after 5 Hz non-event-related NMES was directly related to improved swallowing function. This functional improvement was characterised by a reduction in pharyngeal transit time, swallowing response time and aspiration score. Fraser et al. (2002) further documented that the size of the observed effect was positively related to the intensity of the electrical stimulus, with an approximate 75% of maximal tolerated intensity producing greatest effects.

Additionally, the duration of non-event-related NMES affected the changes in corticobulbar excitability observed post-treatment. Greatest effects were seen

³ The excitatory effect of 5 Hz non-event-related NMES was later replicated by the same group in a different participant cohort, using the same methods (Fraser, Rothwell, Power, Hobson, Thompson & Hamdy, 2003).

after 10 min of non-event-related NMES, whereas stimulation for 5 min or 20 min produced did not produced significant changes. This suggests the existence of a stimulus duration-dependent “window of opportunity” for inducing lasting changes in pharyngeal corticobulbar excitability. Interestingly, the post-treatment effect evolved over a period of several minutes and peaked at 60 min to 90 min post treatment. The authors suggest that mechanisms related to LTP and LTD induction may underlie these changes, as a similar time course is observed for changes of corticobulbar excitability after motor skill training.

In a subgroup of healthy research participants, an increase in the size of the pharyngeal motor map was found 60 min after non-event-related NMES at optimal stimulation parameters (Fraser et al., 2002). In a different cohort, this finding was confirmed by increased activity in the sensorimotor cortex, as measured by the area of activated voxels during fMRI (Fraser et al., 2002).

Together, these observations document that optimal stimulation parameters exist in terms of frequency, duration and intensity of the electrical stimulus. Non-event-related NMES at optimal stimulation parameters increases corticobulbar excitability in health and impairment, and in individuals with dysphagia leads to improved swallowing function. Interestingly, optimal stimulation parameters differed for the two sites of application investigated by Fraser et al. (2002) and Power et al. (2004), suggesting that the observed effects are not only a frequency-specific, but also site-specific. It is important to note that the effects documented in these studies suggest the potential for electrical stimulation to inhibit neural function when it is provided at non-optimal stimulation parameters and that this correlates with decreased swallowing function in healthy individuals (Power et al., 2004).

In a recent study, Oh et al. (2007) investigated the effects of peripheral NMES on swallowing function and measures of cortical map representation of the

cricothyroid muscle. Eight patients, 4 presenting with hemispheric stroke and 4 presenting with brainstem stroke, were treated with 10 hrs of non-event-related NMES to the anterior belly of digastric and thyrohyoid muscles over a two-week period. Electrical stimuli were administered at a frequency of 70 Hz, with a duty cycle of 20 s on and 10 s off and at maximal tolerated intensity. Outcome measures included scores on a dysphagia severity rating scale and a VFSS functional rating scale, as well as TMS-evoked MEP motor threshold and motor map of the cricothyroid muscle. MEPs could only be recorded in 5 of the 8 patients. In 4 of these patients, swallowing function scores improved and VFSS-based swallowing impairment scores decreased significantly post-treatment. This functional improvement was accompanied with an expansion of cortical motor map representation. One patient showed a smaller cortical motor map post-treatment and in this patient, no functional improvements were observed. In all patients, motor threshold, a measure of cortical excitability, did not change in response to treatment. No specific data are reported for the 3 patients that did not display MEPs. However, in a graph plotting swallowing function data of all 8 patients, 6 patients are displayed to have improved swallowing function scores. Therefore, 2 of the patients that did not have recordable MEPs improved in swallowing function.

In agreement with Fraser et al. (2002), this study suggests that non-event-related NMES at the employed stimulation parameters may induce recruitment of extended cortical areas, which may consequently relate to improved swallowing function. This study is limited in that the time post-stroke was not reported; therefore spontaneous recovery in patients in the acute post-stroke phase cannot be ruled out as a confounding factor. Further, outcome measures were not recorded from the muscles that received NMES treatment, which limits the interpretation of a treatment-induced cortical effect.

3.5.4 Literature reviews on the role of NMES in swallowing rehabilitation.

Several publications have been generated regarding the use of NMES in swallowing rehabilitation in the form of a meta-analysis (Carnaby-Mann & Crary, 2007) and literature reviews (Steele, Thrasher & Popovic, 2007; Huckabee & Doeltgen, 2007b).

In a meta-analysis of seven studies, Carnaby-Mann and Crary (2007) documented an overall moderate, statistically significant effect size in favour of the use of NMES treatment as a rehabilitative technique for swallowing rehabilitation. This outcome is based on the inclusion of a single factor in the meta-analysis, the clinical swallowing score, which was the only outcome measurement consistently used across the included studies. The authors claim that despite being influenced by the subjective impression of the examiner, this measure of a patient's swallowing function is widely accepted as a clinical outcome measure. At the same time, the authors list this subjective measurement of swallowing function as a methodological shortcoming of the reviewed studies. The authors further critiqued the lack of controlled trials, control groups, detailed descriptions of intervention and blinded ratings. In summary, the authors conclude that even though the undertaken, preliminary meta-analysis has documented indications that NMES can be an useful tool in swallowing rehabilitation, "recommendations for the use of this technique should be re-evaluated as more data become available" (Carnaby-Mann & Crary, 2007, p. 570).

In their narrative review of the available literature on the effects of NMES on swallowing function, Huckabee and Doeltgen (2007a) conclude that while some preliminary evidence exists for the efficacy of NMES as a viable approach for swallowing rehabilitation for some patients, insufficient evidence exists about the potential for harmful effects, the choice of most beneficial stimulation parameters,

patient groups who would benefit most from this treatment and the precise effects on swallowing biomechanics and neurophysiology. Therefore, it was concluded that “application of this technique in the patient population is considered premature and should therefore not be utilised in the treatment of swallowing disorders until further evidence is available” (Huckabee and Doeltgen, 2007a, p. 11). Steele et al. (2007) reached a similar conclusion in a review of the literature on electrical stimulation approaches in swallowing rehabilitation. The authors stated that due to a lack of evidence for the effectiveness and safety of this treatment, “electric stimulation of the oropharyngeal swallowing process should not be adopted in clinical settings until proper evidence based results demonstrate its efficacy” (Steele et al., 2007, p. 14).

3.6 Terminology

A variety of terms and definitions have been used throughout the literature for the application of electrical current to human nerve and muscle tissue as a rehabilitative treatment approach. Their inconsistent use contributes to the lack of clarity in the employed methodologies across research studies. The American Physical Therapy Association (APTA) has provided definitions for some of these terms. Transcutaneous electrical nerve stimulation (TENS) describes the application of electrical current through the skin for pain control (APTA, 1990), whereas neuromuscular electrical stimulation (NMES) is identified with the “external control of innervated, but paretic or paralytic muscles by electrical stimulation of the corresponding intact peripheral nerves” (in Baker et al., 1993, p. 5). However, many terms are used in publications without an exact definition of their precise meaning. Often, terms describe the context during which the electrical stimulation is provided, for example “functional” or “synchronised”. Similarly, some terms reflect the

medium to which the electric current is applied, for example “transcutaneous” or “surface”.

A similar problem is evident when reviewing the body of literature reporting the effects of NMES in swallowing rehabilitation. Researchers have used a variety of treatment paradigms and have defined terms in different ways. Terms used previously include “transcutaneous electrical stimulation (TES)” (Blumenfeld et al., 2006), “neuromuscular electrical stimulation (NMES)” (Suiter et al., 2006; Buelow, Speyer, Baijens, Woisard & Ekberg, 2008), “functional electrical stimulation (FES)” (Burnett et al., 2005), “transcutaneous NMES” (Carnaby-Mann & Crary, 2008; Shaw, Sechtem, Searl, Keller, Rawi & Dowdy, 2007), “synchronised electrical stimulation (SES)” (Leelamanit et al., 2002), “surface electrical stimulation” (Humbert et al., 2006; Ludlow et al., 2007) or simply “electrical stimulation” or “estim” (Oh, Kim & Paik, 2007). The inconsistency of definitions and methodological approaches makes it difficult to directly compare research outcomes, to interpret the data at a meta-level and ultimately to draw compelling conclusions about the efficacy of NMES, particularly for the rehabilitation of impaired swallowing.

3.7: Risks and Contraindications

Because of the described mode of operation of electrical stimulation, in particular because of the high intensity electrical current introduced into the biologic tissue, there are potential risks to the application of NMES in humans.

Contraindications include pacemakers, superficial metal implants or orthotics, skin breakdown, cancer, history of cardiac or seizure disorder, impaired peripheral nerve conduction systems and pregnancy (Barker, Jalinous & Freeston, 1985). A specific potential risk factor for using NMES in swallowing rehabilitation may be the site of stimulus application, which in this context would logically be in the face and neck

region. Given the proximity of major arteries supplying the brain and of cranial nerves influencing respiratory function, this may be a justified concern. Indeed, warning labels on NMES devices cleared by the USA Food and Drug Administration (FDA) state that “severe spasm of the laryngeal and pharyngeal muscles may occur when the electrodes are positioned over the neck or mouth. The contractions may be strong enough to close the airway or cause difficulty in breathing” (FDA, 1999, Attachment I). In 2001, the FDA approved the use of a newly developed NMES stimulator, the VitalStim™, for use in swallowing rehabilitation. A warning label accompanied the approval of this device: “The long term effects of chronic electrical stimulation are unknown. Stimulation should not be applied over the carotid sinus nerves. If electrodes are placed improperly and the unit is not used with the recommended frequency, intensity and pulse rate, it may cause laryngeal or pharyngeal spasm.” (FDA, 2001, p. 103).

In the light of these potential contraindications and due to the lack of a clear understanding of the mechanisms governing the precise effects of NMES, there is a pressing need to thoroughly investigate the effects of NMES on swallowing safety, biomechanics and underlying neurophysiology. Recent years have seen a number of investigations evaluate these effects; however, many questions still remain to be answered. As NMES has only recently emerged as a rehabilitative approach in the area of swallowing rehabilitation, reviewing the literature of an area that has used NMES for a longer period of time, the area of physical rehabilitation medicine may assist in developing a better understanding of the mechanisms governing the effects of NMES on the human neuromuscular system.

3.8: Summary

Introduction of electrical current into biological tissue alters the composition of the cell membrane and if of sufficient intensity, initiates the generation and transmission of an action potential. Depending on the intensity of the electrical current, sensory or both sensory and motor nerve fibres can be activated. This results in subsequent sensory perception of the stimulus, which is accompanied by a motor response, if the electrical stimulus is of adequate intensity. The generation and chemical synaptic transmission of an action potential in response to NMES involves the same processes of neurosecretion and chemoreception than endogenous excitation. However, the exogenously initiated muscle contraction differs from the intrinsically generated motor response in the ordering of muscle fibre recruitment and the stimulus intensity required to produce muscle contraction, deeming it metabolically more demanding.

The research reviewed in this chapter has documented potential clinical and neurophysiological benefits gained from NMES of the corticospinal and corticobulbar system. In swallowing rehabilitation, these benefits may include increased swallowing efficiency and safety (e.g. Freed et al., 2001; Leelamanit et al., 2002), enhanced swallowing biomechanics (Carnaby-Mann & Crary, 2008) and increased corticobulbar excitability (Fraser et al., 2002; Power et al., 2004). However, several studies have also identified negative effects of NMES on measures related to swallowing, in particular a decrease in corticobulbar excitability after NMES provided at certain stimulus frequencies (Fraser et al., 2002; Power et al., 2004) and a directly related degeneration of swallowing function in healthy research participants (Power et al., 2004). Therefore, further thorough investigation is warranted into the precise mechanisms that underlie the NMES-induced changes in swallowing neurophysiology and consequently swallowing function. The identified

potential for harmful effects induced by NMES provided at non-optimal treatment parameters underscores the importance of gaining a better understanding of these mechanisms.

Due to its relative clinical in-accessibility, pharyngeal and oesophageal NMES may not be a suitable approach for the wide application of this technique in patient populations. Indeed, most research and current clinical applications focus on the submental and laryngeal musculature as targets of NMES intervention. However no research has established which NMES parameters are optimal for inducing beneficial and lasting changes in corticobulbar excitability when stimulating this muscle group and how these changes relate to swallowing function.

Chapter 4: Transcranial Stimulation of the Human Brain

As summarised in the chapter above, several researchers have used MEPs as an outcome measure to document the effects of NMES on swallowing neurophysiology. The following chapter explores the use of this measurement tool as an outcome measure for swallowing neurophysiology as a means of commenting on previous literature and establishing its feasibility for future research.

4.1: Historical Development

4.1.1: Electrical brain stimulation. The study of the human brain and its underlying neurophysiology has fascinated researchers for many centuries. The basis of modern brain research was laid by the early experiments of Galvani who demonstrated that animal muscle tissue preparations could be excited to contract by applying zinc and copper electrodes to the nerve and muscle. Soon after this discovery, Volta demonstrated that the muscle contractions observed by Galvani were caused by the different electrical properties of the zinc and copper electrodes. In subsequent years, Volta's work led to the invention of the first basic battery, the "Voltaic cell".

In 1870, Fritsch and Hitzig were the first to electrically stimulate the dog brain and reported that brief twitches could be evoked in the muscles contralateral to the site of stimulation. These responses were observed when a relatively small area of the frontal part of the brain was stimulated. A few years later, Ferrier confirmed the observation made by Fritsch and Hitzig by showing in a series of animal experiments that electrical stimulation of certain parts of the brain produced muscle twitches on the contralateral side of the body (Ferrier, 1873). He also documented that different parts of this motor area represented specific muscles of the body.

Bartholow was the first to document electrical stimulation of the human cortex in a patient who presented with open ulcerations over the parietal cortices (Bartholow, 1874). By means of two needle electrodes, Bartholow demonstrated that movements could be evoked on the contralateral side in response to electrical stimulation of the cortex. The neurosurgeons Penfield and Jasper (1954) carried this knowledge further and systematically mapped the motor (and sensory) areas of the human brain. This research subsequently produced the well-known homunculus, a schematic representation of body parts on the surface of the precentral gyrus. Today, electrical stimulation of the brain is in widespread clinical use, especially during intra-operative monitoring of functional corticospinal connectivity (Slimp, 2004).

While the application of electrical currents through surface or needle electrodes is very effective for the stimulation of peripheral nerves that are close to the skin surface (Chapter 3), the stimulation of cortical tissue underlying the bony skull requires high voltage stimuli (Merton & Morton, 1980). These stimuli cause intense cutaneous pain, making this procedure uncomfortable, and preventing it from becoming established in widespread clinical use. The subsequent development of modern magnetic brain stimulators overcame this limitation (Barker et al., 1985).

4.1.2: Magnetic brain stimulation. Unlike electrical stimulation, magnetic stimulation uses a brief magnetic field to induce the flow of current in the tissue it is applied to. However, both electrical and magnetic brain stimulation techniques rely on the same cellular mechanisms that respond to electric current flowing across a cell membrane, which changes the relative polarity between the intra- and extra-cellular environments. If of sufficient magnitude, this change in polarity differential depolarises the cell membrane and initiates an action potential, which propagates along the axon (Bear et al., 2006) (see Chapter 3 for a more detailed review). The

first application of magnetic stimulation was documented by d'Arsonval in 1896 who reported that a changing magnetic field can induce electric currents in human muscle and nerve tissue (Ebmeier & Lappin, 2001). Silvanus P. Thompson (1910) later reported the generation of phosphenes and vertigo when a participant's head was moved in and out of a magnetic field (Figure 4).

Figure 4.

Silvanus Thompson was one of the first to document the effects of magnetic fields on the human brain.



It was not until 1985 that the early work of these researchers led to the development of the first magnetic stimulator that was capable of stimulating focal cortical regions through the intact skull without generating a painful sensation on the scalp (Barker et al., 1985). Magnetic stimulation of the cortex was achieved with a coil of wire that produced a short-lasting magnetic field. When positioned over the

vertex, hand movements could be observed and electrical potentials recorded at the abductor digiti minimi muscle of the contralateral side of the body. Because of its easy use, painless application and, most importantly, potential to uncover many hidden processes of the intact and impaired central nervous system, TMS has today become a frequently used and heavily researched assessment, research and even treatment tool.

4.2: Physical Principles and Technical Characteristics

Three principles of electromagnetism form the basis of TMS. First, Ampere's law states that electric current flowing through a conductor (primary) produces a magnetic field. The intensity of the magnetic field produced is proportional to the current I (in Ampere) that flows through the primary. In a coil of wire with the radius r , the magnetic field is generated perpendicular to the current flow, and its strength H is calculated as follows:

$$H = I / 2r$$

The experiments by Michael Faraday in 1831 form the basis of the second important principle of electromagnetic stimulation. According to Faraday's research, an electrical current can be induced in a conductive medium (secondary circuit) by a changing magnetic field, either by moving the secondary circuit in or out of a constant magnetic field or by changing the intensity of the magnetic field produced by the primary over a short period of time. The magnitude of the induced electrical

field E^4 (measured in Volts) is dependent on the rate of change of the magnetic field strength B over time t .

$$E \approx -dB/dt$$

Transcranial magnetic stimulation of the human cortex is based on changes in magnetic field strength. The primary circuit is the stimulation coil, which produces a rapidly changing magnetic field. Underlying neural tissues form the secondary circuit into which the current is induced (Barker et al., 1985).

The induction of electrical current in a secondary circuit depends on a number of factors, including the strength of the magnetic field, its time course of change and the permeability of the matter it penetrates. Substances such as water, air or human tissue have a permeability constant of approximately 1, and therefore pose only little resistance to the penetrating magnetic field (Brandt, Ploner & Meyer, 1997). However, materials such as metal provide much higher resistance and therefore pose a much larger risk to be affected by the magnetic field. For this reason, individuals with metallic implants are generally excluded from TMS procedures for safety reasons (Keel, Smith & Wassermann, 2000).

Thirdly, according to the Maxwell equations, the magnitude of the induced current E changes at different angles to the magnetic field that induces it:

$$E \approx \frac{dB}{dt} \sin\alpha$$

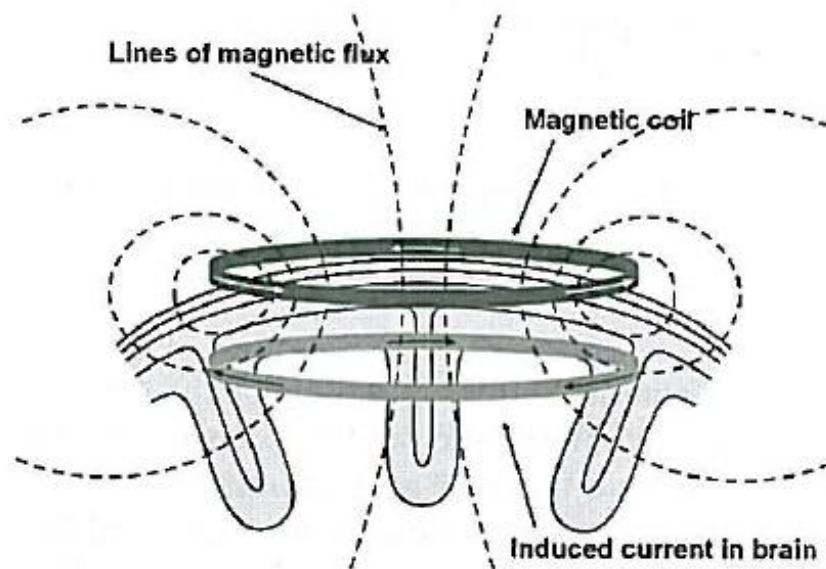
where $\sin \alpha$ describes the angle between the secondary circuit and the magnetic field. Maximal current induction occurs when $\sin \alpha$ equals 1, which describes the

⁴ Note the negative prefix, indicating that the polarity of the induced current E is opposite to that of the magnetic field that induces it. This particular phenomenon is also described as Lenz's law.

phenomenon that maximal current will be induced in a secondary circuit that is located perpendicular to the magnetic field. In regards to the magnetic stimulation of the cortex this means that cortical structures, which are oriented in parallel to the magnetic coil, will be excited maximally. Figure 5 displays the induction of eddy currents in the brain, and their relative orientation to the magnetic field and the stimulating coil.

Figure 5.

Induction of eddy currents in the brain by TMS. Note the perpendicular orientation of the magnetic field relative to the magnetic coil (Ampere's law), the perpendicular orientation of the induced electrical field relative to the magnetic field (Maxwell equations), and the direction of the induced eddy current opposing the direction of the (primary) electric field in the stimulation coil (Lenz's law) (Hallett , 2000).



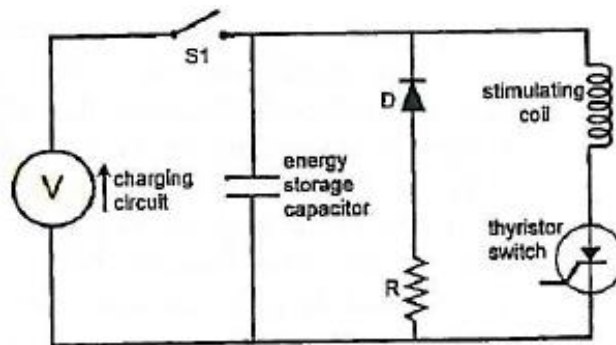
4.3: Components and Technical Design

Transcranial magnetic stimulators consist of two main components: a power device, consisting of a capacitor, thyristor switch and resistor, and a coil of wires,

which is connected to the power device via a cable. Figure 6 illustrates a schematic diagram of a standard magnetic stimulator. Much like a battery, the capacitor in the power device can store high voltage. The thyristor switch acts as a gate between the capacitor and the stimulating coil. When triggered, a large electrical current is rapidly charged through the coil, generating a strong magnetic field. The approximate rise time of the usually monophasic magnetic field pulse is 100 μs , which decays back to zero over about 800 μs (Figure 7). As the magnetic field collapses, the electrical energy returns from the coil to the stimulating device and dissipates as heat in the resistor R (Barker, 1999).

Figure 6.

Schematic diagram of a magnetic stimulator (Barker, 1999).

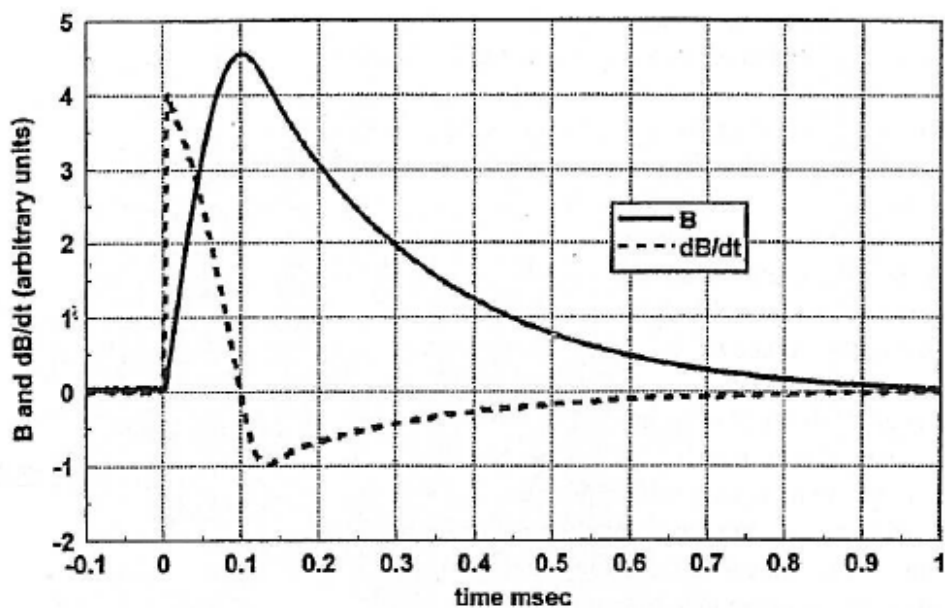


4.3.1 Induction of current in neural tissue. The scalp, skull and surrounding cerebrospinal fluid pose little resistance to the magnetic field (Davey, 2008). It therefore penetrates these structures with little attenuation and induces eddy currents (i.e. induced currents) in the area below the stimulation coil, which in turn stimulate the surrounding neural tissue. The time course of the magnetic field produced by most single-pulse magnetic stimulators and the eddy currents it induces is depicted in Figure 7. The magnetic field also induces currents in the scalp; however, these

currents are minimal and therefore cause substantially less discomfort than the large currents induced by transcranial electrical stimulation (Barker, 1999).

Figure 7.

Time course of the magnetic field (solid line) and induction of the resulting eddy current (dotted line) (Barker, 1999).

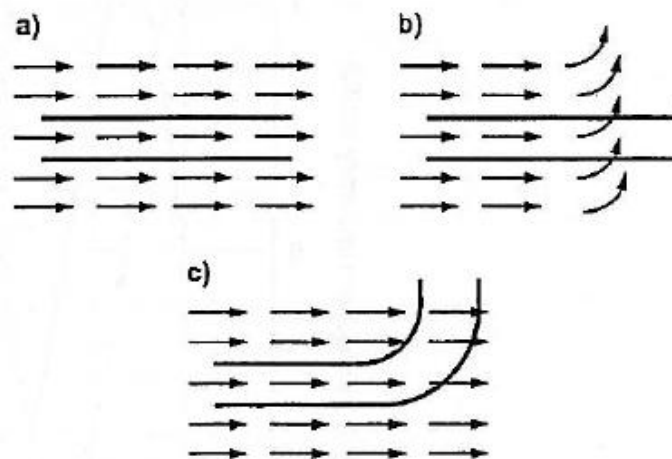


A nerve fibre is stimulated at that point along its axon at which sufficient current causes depolarisation of the cell membrane (Barker, 1999). As described in more detail in Chapter 3, during electrical stimulation this point is likely to be close to the cathode. For magnetic stimulation, the site of stimulation is less well defined. To stimulate an axon, a potential difference must exist between two points along its length. The degree of stimulation is proportional to the rate of change between these points of the electric field, a function that is also known as the *spatial derivative* (Barker, 1999). If the electric field induced by magnetic stimulation is uniform and is oriented parallel to the nerve, then current flow will occur to an equal degree

inside and outside of the axon, and no current will flow across its membrane (Rothwell, 1997; Barker, 1999). Therefore, no depolarisation will occur (Figure 8a). If a nerve is not completely parallel to the electric field, as would most likely be the case in the complex pattern of neurons in the brain, then depolarisation of the axon membrane is induced where the axon bends across the electric field lines (Rothwell, 1997; Barker, 1999) (Figure 8c). Similarly, if the current flow changes along the length of a nerve (Figure 8b), then current flow will be induced where the electric field lines cross the nerve membrane. An axon may also be stimulated when it runs through an area of tissue of different conductive properties, for example when emerging from a bony foramen (Maccabee, Amassian, Eberle & Cracco, 1993).

Figure 8.

Schematic illustration of (a) a uniform electric field along a parallel nerve fibre (inducing no transmembrane current, (b) current flow of an electric field shifting along the length of the axon, inducing transmembrane current and (c) a uniform electric field across a nerve bend, inducing transmembrane current (Barker, 1999).



The macroscopic neuronal orientation is therefore an important factor in the induction of electrical current in human brain tissue. As described above, maximal

induction occurs in neurons that are oriented parallel to the stimulation coil, for example, neurons located within a sulcus. Most neurons in the human motor cortex, however, are extrasulcal, descending neurons of the pyramidal system, which are oriented in a more or less perpendicular plane to the TMS coil. Therefore, TMS is thought to excite these neurons indirectly, via horizontal interneurons (Meyer, 1992). This hypothesis, which is now generally accepted, is based on observations of differences between MEP onset latencies recorded in response to transcranial electrical stimulation (TES) and TMS.

Motor evoked potentials following TES generally occur approximately 2 ms earlier than MEPs evoked by TMS. Transcranial electric stimulation evokes a sequence of excitatory volleys in pyramidal tract neurons (Terao & Ugawa, 2002), the first being the so-called D-wave (direct wave), followed by later I-waves (indirect waves). The D-wave results from direct activation of the neuronal axon, most likely occurring not directly at the cell body, but a number of nodes proximally (Patton & Amassian, 1954). This conclusion was drawn on the basis of absent influences of electrical sensory stimulation (Amassian, Stewart, Quirk & Rosenthal, 1987) or voluntary activity (Day, Rothwell, Thompson, Dick, Cowan, Berardelli et al., 1987) on motor threshold for TES (see review by Rothwell, 1997). At sufficiently high stimulus intensities, the later I-waves are generated, following the D-wave at approximately 1.5 ms intervals (Boyd, Rothwell, Cowan, Webb, Morley, Asselman et al., 1986). The exact mechanisms underlying this phenomenon are unknown, however, I-waves are thought to be related to repetitive firing of pyramidal motor neurons, with the delay in onset latency resulting from transsynaptic activation within the pyramidal tract system (Rothwell, 1997; Terao & Ugawa, 2002). The onset latencies of MEPs evoked by TMS are delayed by a similar interval, and the geographic orientation of pyramidal motor neurons within

the primary motor cortex substantially limits direct neuronal activation by TMS. It is therefore thought that TMS induces transsynaptic cortical excitation, essentially producing I-waves. This hypothesis is further supported by reports that MEPs evoked by TMS are sensitive to changes in cortical excitability, whereas MEPs evoked by TES, representing primarily D-waves, are not (Maertens de Noordhout, Rothwell, Day, Dressler, Nakashima, Thompson et al., 1992).

Two types of coils are most commonly used for magnetic stimulation of the cortex: circular coils or figure-of-8 coils. Due to their different geometry, the magnetic fields they produce, and hence the shape of the electric fields they induce, vary. Circular coils were the first to be used. They have the advantage of being relatively easily placed in a stable position over the scalp or peripheral nerve of interest. However, a large degree of uncertainty exists as to the exact location of stimulation. As shown in Figure 9, a straight nerve positioned under a circular coil will most likely be depolarised in region A and hyperpolarised in region B. As Barker (1999) describes it, “the regions can be thought of, by analogy with electrical stimulation, as a “virtual cathode” and a “virtual anode” respectively” (p.12). Because of the uncertainty about the exact orientation of the underlying nerve fibres, the exact site of stimulation cannot be easily identified.

Figure 9.

Rate of change of the induced electric field. Depolarisation of the depicted nerve is most likely to occur in region A, whereas hyperpolarisation is more likely to occur in region B (Barker, 1999).

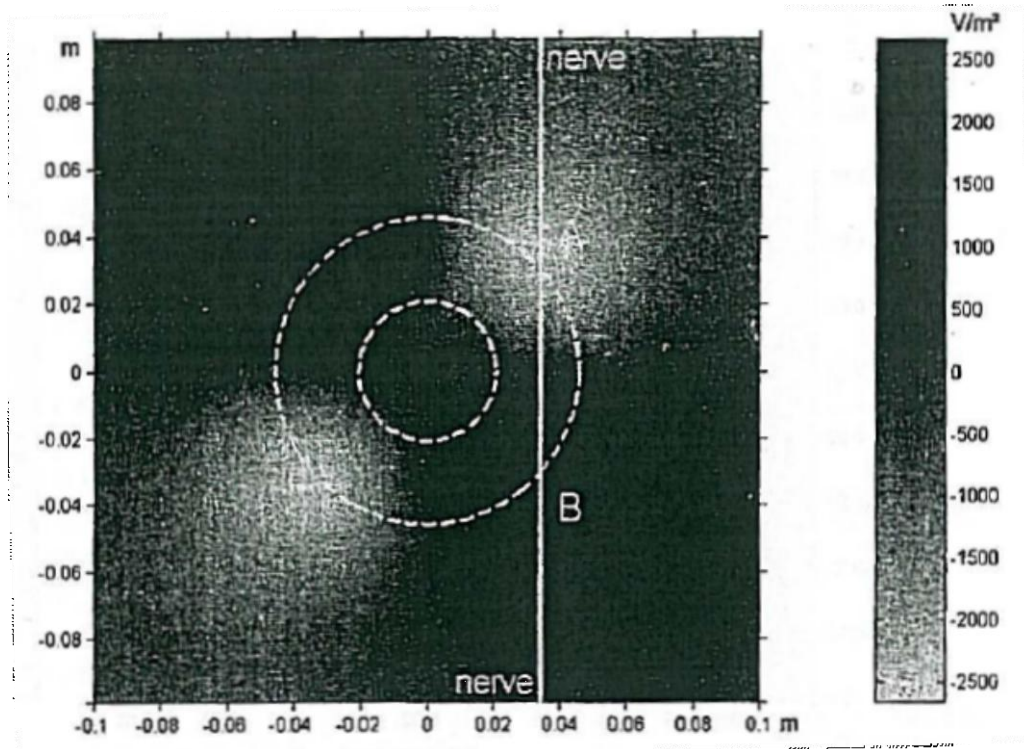
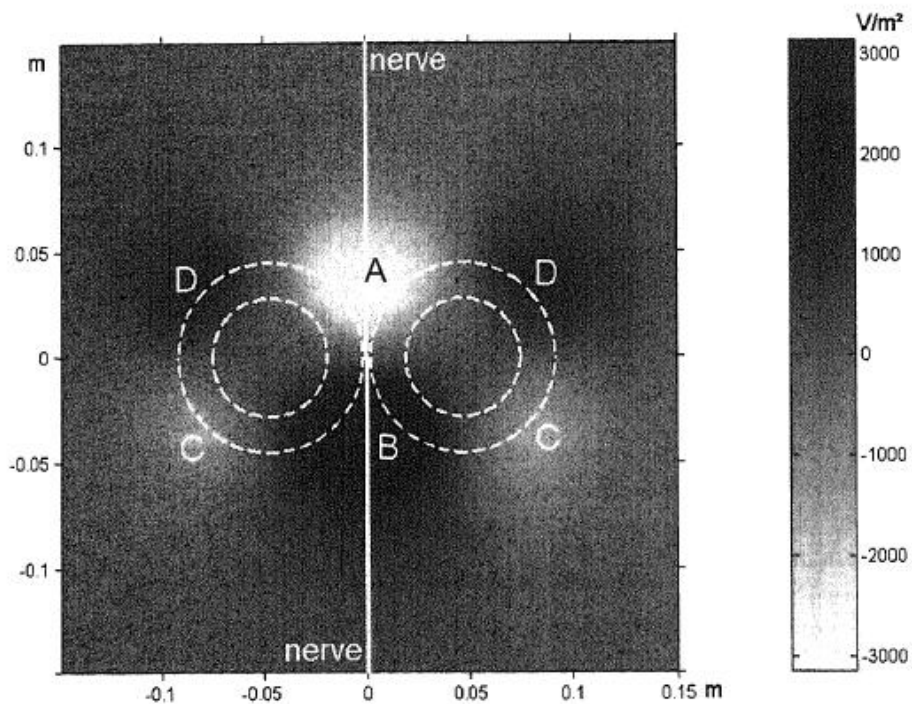


Figure-of-8 coils consist of two circular coils placed side by side. They are connected to the stimulator such that the direction of current flow in one coil will be opposite to that of the other coil. At the junction of the two circular coils, current will flow in the same direction, thus the induced electric fields will combine and the strength of the induced electric field (and current) increases nearly two-fold. This geometry has the advantage of decreasing the uncertainty of the site of stimulation. As shown in Figure 10, the maximum and minimum rate of change of the electric field, [i.e. the virtual cathode (A) and anode (B)] is located at midline between the two circular coils. Stimulation will therefore most likely occur at the centre of the figure-of-8 array.

Figure 10.

Rate of change of the electric field induced by a figure-of-8 coil. Note that stimulation is most likely to occur in region A (virtual cathode) than region B (virtual anode). Secondary peaks C and D at the sides of the coil are typically only half the amplitude of the peaks at midline (Barker, 1999).



In summary, depolarisation of an axon occurs when the induced electrical current is of adequate intensity to depolarise the axon at any point along its length. This point is determined by the relative orientation of the axon to the induced electric currents. If polarisation occurs, an action potential is generated and propagated along the axon according to known physiological processes.

4.4 Motor Evoked Potentials

Transcranial magnetic stimulation of the motor cortex can evoke electric responses in contralateral muscles, known as the motor evoked potential, or MEP (Barker, 1999). These responses originate from the depolarisation of corticospinal or

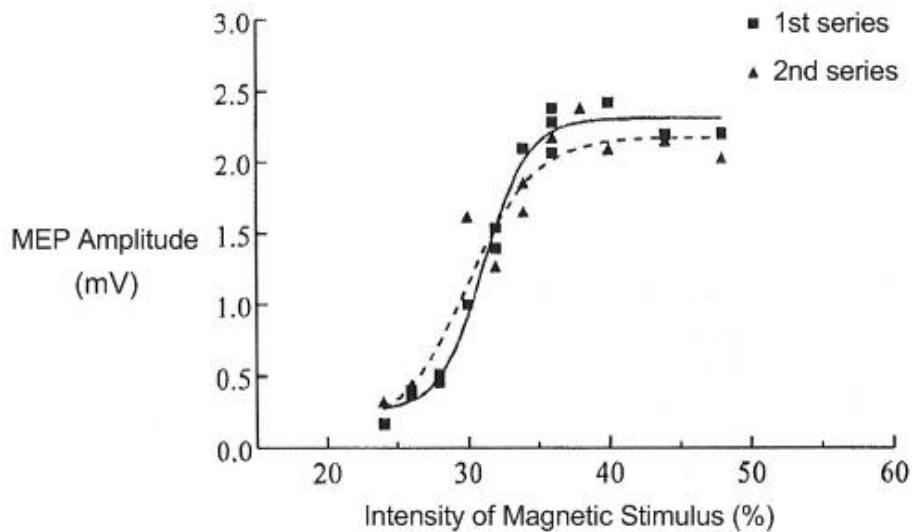
corticobulbar motor neurons by the TMS-induced electric current (Maeda & Pascual-Leone, 2003). A variety of MEP parameters can be measured, most often including amplitude and onset latency, but also stimulation threshold (motor threshold), silent period and others. In this review, the parameters of MEP amplitude and onset latency will be discussed.

The amplitude of the MEP reflects the level of excitability of the corticospinal or corticobulbar system, in particular the number of activated corticospinal or corticobulbar motor neurons projecting to lower motor neuron pools, providing a quantifiable measure of neural pathway excitability (Bestmann, 2007). Motor evoked potentials can be easily measured from the peripheral musculature with surface or needle EMG electrodes. The investigation of cortical motor areas has therefore progressed faster than the evaluation of other brain areas, for example those involved in cognitive processes, for which measuring and quantifying evoked responses is more difficult.

MEP amplitude changes as a function of TMS intensity, that is, increasing stimulus intensity will produce larger MEPs, likely due to excitation of increasing numbers of corticospinal or corticobulbar motor neurons (Roesler & Magistris, 2008). This phenomenon is analogous to increases in the size of the muscle response induced by peripheral electrical stimulation, which occurs due to increasing recruitment of larger numbers of motor nerve fibres (Roesler & Magistris, 2008). Figure 11 displays the sigmoidal relationship between TMS intensity and MEP amplitude in the tibialis anterior muscle.

Figure 11.

Sigmoidal relationship between TMS intensity and MEP amplitude in the tibialis anterior muscle during approximately 10% of maximal muscle contraction. The two waveforms represent data collected from one individual during two recording sessions, 1.5 hr apart (Devanne, Lavoie & Capaday, 1997).



Considerable inter-individual differences have been observed regarding the degree of facilitation in response to increasing TMS intensity. This stimulus-response relationship also varies across different muscles within the same individual (Ziemann, Ilic, Alle & Meitzschel, 2004). Because MEP amplitude depends on the intensity of the magnetic field, it is also susceptible to changes in the positioning of the coil, that is, the intensity and orientation of the induced electrical current flow in the brain. Early research using circular TMS coils demonstrated that when located over the vertex, clockwise current orientation preferentially activated the right hemisphere, whereas counter clockwise current orientation mainly stimulated the left hemisphere (Hess, Mills & Murray, 1987). Focal cortical stimulation with figure-of-8 coils, allowing more precise stimulation of smaller cortical areas such as those used in brain mapping experiments and research investigating cortical

representation of isolated muscles, requires careful positioning of the coil over the motor representation of the target muscle. For hand and facial muscles, Brasil-Neto, Cohen, Panizza, Nilsson, Roth & Hallett (1992) demonstrated that optimal stimulation was achieved when the coil was oriented perpendicular to the central sulcus, whereas an orientation perpendicular to the longitudinal fissure was demonstrated to be most beneficial for the leg muscles (Roesler, Hess, Heckmann & Ludin, 1989). Differing optimal coil orientations are thought to relate to different orientations of underlying neurons in the investigated cortical motor areas.

The onset latency of the MEP reflects the time between the stimulation of the motor cortex by TMS and the onset of the MEP recorded from the target muscle. It increases relative to the distance of the muscle under investigation from the motor cortex, ranging from approximately 8 ms for the facial muscles to approximately 43 ms for the lower limb muscles (Rothwell, Thompson, Day, Boyd & Marsden, 1991). MEP onset latency is affected by various phenomena, for example muscle pre-activation (see section *4.4.1 Facilitation of MEP parameters* below). Onset latency measurement can also be used to identify central motor conduction time (CMCT). Generally, MEP onset latency includes both a central component (latency from motor cortex to spinal or brainstem motor neuron) and a peripheral component (latency from motor neuron to target muscle). In order to identify abnormalities of the central, pyramidal motor pathways, CMCT can be estimated by subtracting peripheral motor conduction time from MEP onset latency. CMCT is an important measure in the clinical use of MEPs, in particular because of its ability to quantify damage to the pyramidal pathways, for example in neurodegenerative disorders.

4.4.1: Facilitation of MEP parameters. Both the amplitude and onset latency of the MEP can be facilitated. Facilitation occurs in particular during

voluntary background activation of the target muscles, but can also be induced by other factors including conditioning electrical stimuli (such as IPAS), peripheral cutaneous or muscle sensory input, or even imagining a movement or muscle contraction (Roesler & Magistris, 2008). Lowering of motor neuron excitation thresholds, and subsequent activation of a greater number of motor neurons by TMS, is thought to be the primary mechanism underlying this facilitation. Interestingly, the degree of facilitation seems to be task-dependent. Datta, Harrison and Stephens (1989) documented that healthy research participants displayed larger MEPs in the first dorsal interosseus muscle during a simple abduction task of the index finger than during a power grip task. Hasegawa, Kasai, Tsuji and Yahagi (2001) reported that MEP amplitudes increased significantly more during a precision grip than during a power grip. Similarly, Flament, Goldsmith, Buckley and Lemon (1993) showed that MEP facilitation was larger during a series of complex motor tasks compared to simple abduction of the index finger. Additionally, MEPs of the first dorsal interosseus muscle increased in one hand when the same muscle of the other hand was contracted (Stedman, Davey & Ellaway, 1998). Similarly, performing complex finger tasks with one hand (task-hand) affects MEPs recorded from the other hand (test-hand). This facilitation was found to be larger during complex finger tasks than mild tonic contraction of the task-hand (Ziemann & Hallett, 2001). Transcallosal pathways have been suggested to be involved in this facilitation of MEPs recorded from muscles contralateral to the task-hand (Ziemann and Hallett, 2001).

In contrast to the facilitation induced by contralateral muscle contraction, inhibitory effects may also be mediated via transcallosal pathways. When a conditioning, inhibitory stimulus is given to the motor cortex of one hemisphere 10 to 15 ms before a test-stimulus is given over the motor cortex of the other

hemisphere, the amplitude of the MEP in response to the test-stimulus is decreased (Ferbert, Priori, Rothwell, Day, Colebatch & Marsden, 1992). Facilitation or inhibition of contralateral motor pathways have important implications for individuals suffering from the consequences of hemispheric stroke, as use of the contralateral, non-affected hand may affect the level of excitability of the ipsilateral (affected) hemisphere. This question was addressed by Woldag, Lukhaup, Renner and Hummelsheim (2004), who documented that voluntary contraction of the unaffected hand had no inhibitory effect on the ipsilateral hemisphere in either healthy research participants or individuals post stroke.

Similar to MEP amplitude, onset latency can be facilitated by voluntary muscle pre-activation. This has been documented to reduce onset latencies by up to 3 ms (Rossini, Barker, Berardelli, Caramia, Caruso, Cracco et al., 1994). Spinal and cortical mechanisms are thought to be responsible for the decrease in onset latency. Facilitation may occur via afferent peripheral input from muscle receptors, contributing to: (a) greater motor neuron excitability, ultimately resulting in a greater number of motor neurons activated by TMS, (b) increased excitability of alpha motor neurons in the spinal cord or (c) a combination of both. Both factors are likely to contribute to a faster depolarisation of the alpha motor neuron during muscle contraction (Sandbrink, 2008). When facilitation or inhibition occur in response to other mechanisms, such as somatosensory stimulation, differentiation of the exact level at which changes occur in the CNS is an important prerequisite for the interpretation of research results (Rothwell et al., 1991). Measurement of CMCT may provide some information about the level at which changes in excitability occur.

4.4.2: Variability of MEP parameters. The ability to evoke MEPs varies widely across individuals (Wassermann, 2008). Some individuals display readily discernable MEPs of large amplitude, whereas in others, small or even no MEPs can be recorded at all, even at high TMS intensities. This phenomenon has been described for the biceps brachii muscle in response to TMS of the corresponding area of the contralateral BA4 (Ziemann et al., 1998) and is also reflected by reports that preactivation is necessary to evoke discernable MEPs in the facial muscles (Cruccu, Berardelli, Inghilleri & Manfredi, 1990; McMillan, Watson & Walshaw, 1998a).

Beyond these inter-individual differences in the ability to evoke MEPs, certain MEP parameters, especially MEP amplitude, vary widely across individuals and even within individuals (Wassermann, 2008). Factors such as age, gross anatomy, genetics or behavioural traits have been discussed as contributors to inter-individual variations. Other factors, including experimental context or menstrual cycle, may contribute to intra-individual variability.

No conclusive data have been presented in regard to the effects of age on MEP parameters. One study has reported greater intracortical inhibition in a younger participant cohort (Peinemann, Lehner, Conrad & Siebner, 2001), whereas another study documented the opposite effect (Kossev, Schrader, Dauper, Dengler & Rollnik, 2002). Wassermann (2002) reported no age-related differences in regard to MEP threshold. Distance from the scalp to the motor cortex has been documented to increase MEP threshold in healthy individuals, as determined by TMS and structural MRI (McConnell, Nahas, Shastri, Lorberbaum, Kozel, Bohning et al., 2001). Stokes, Chambers, Gould, Henderson, Jenko, Allen et al. (2005) documented similar findings with a linear increase in motor threshold when the coil was moved away from the scalp in a range of 1cm. Genetic factors have also been shown to influence

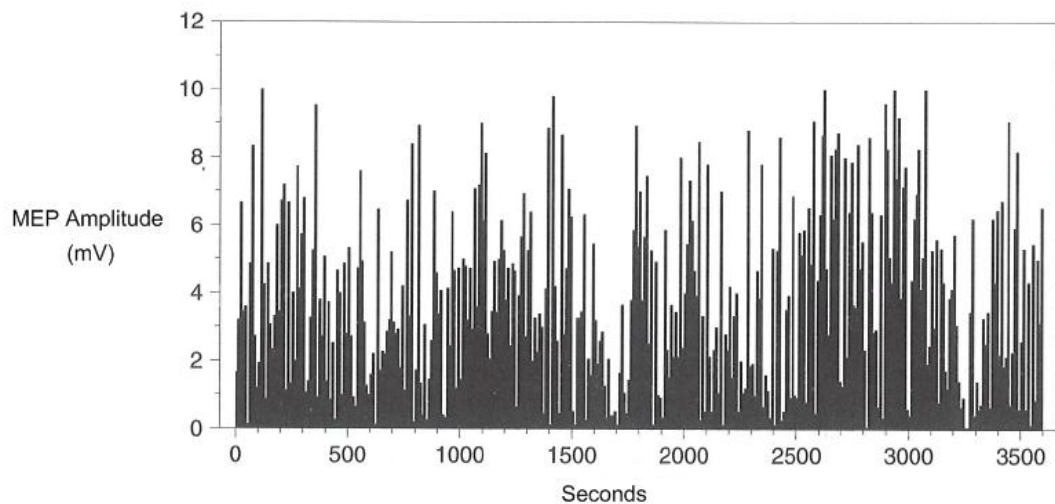
MEP parameters. For example, increased corticospinal excitability (Ikoma, Samii, Meruceri, Wassermann & Hallett, 1996) and decreased intracortical inhibition (Ridding, Sheean, Rothwell, Inzelberg & Kujirai, 1995) have been documented in individuals with dystonia. These observations were also made in individuals who were phenotypically asymptomatic, but carried the responsible DYT1 gene mutation (Edwards, Huang, Wood, Rothwell & Bhatia, 2003). Other gene expressions have been linked to decreased MEP facilitation after motor training (Kleim, Chang, Pringle, Schallert, Procaccio, Jimenez et al., 2006), and sibling pairs have been shown to display significantly correlated MEP thresholds in the dominant hemisphere (Wassermann, 2002). In regard to personality traits, a significant correlation was found between intracortical inhibition and the trend to experience negative emotions or anxiety (Wassermann, Greenberg, Nguyen & Murphy, 2001).

Intra-individual variability has been shown to follow a cyclic pattern, with substantial changes in MEP amplitude observed over a period of seconds or minutes (Figure 12). These changes may be linked to variations in cardiac or respiratory cycles; however, correlations have not yet been clearly identified (Fillipi, Oliveri, Vernieri, Pasqualetti & Rossini, 2000). Further, changes in visual input by eye closure or blindfolding have been shown to increase MEP amplitude (Leon-Sarmiento, Bara-Jimenez & Wassermann, 2005). Anticipation of task performance has been demonstrated to increase MEP amplitude when TMS was performed over the left hemisphere (Seyal, Mull, Bhullar, Ahmad & Gage, 1999). Hormonal changes, in particular in the context of the menstrual cycle in women, have been suggested to contribute to intra-individual differences in cortical responses to TMS; however, no clear links have been established (Smith, Keel, Greenberg, Adams, Schmidt, Rubinow et al., 1999; Smith, Adams, Schmidt, Rubinow & Wassermann, 2003).

In summary, responses to cortical TMS are susceptible to changes in neuronal excitability, some of which occur intrinsically whereas others depend on the experimental context (visual input, task anticipation). Some changes in neuronal excitability further depend on genetic pre-disposition or reflect patterns of underlying neurobehavioural substrates.

Figure 12.

Variability of MEP amplitude recorded from the first dorsal interosseus muscle across a 1 hr period. One MEP recorded every 10 s (Wassermann, 2008).



4.4.3: Effect of training on MEP amplitude. It has been shown that MEP amplitude increases in response to practice of a novel motor task (Bueteffisch & Cohen, 2008). This use-dependent change is only observed in the muscle(s) involved in the task, and does not extend to antagonistic (Bueteffisch, Davis, Wise Sawaki, Kopylev, Classen et al., 2000) or completely uninvolved muscles (Muellbacher, Ziemann, Boroojerdi, Cohen & Hallett, 2001). For example, MEPs recorded from the extensor pollicis brevis muscle have been reported to increase after a thumb extension exercise, whereas MEPs recorded from the antagonistic

flexor pollicis brevis muscle decreased. This supports the view that the human motor cortex is involved in the acquisition of new motor skills (Muellbacher, Richards & Ziemann, 2002a). Interestingly, MEP amplitude increases that are associated with skill acquisition dissipate after the skill has been acquired or over-learned (Pascual-Leone, Grafman & Hallett, 1994; Muellbacher, Ziemann & Wissel, 2002b). A similar pattern has been documented for use-dependent changes in motor map areas, which increased during practice of a complex motor sequence, and returned to baseline once the task was explicitly mastered (Pascual-Leone et al., 1994). Taken together, changes in MEP amplitude and motor map area provide useful information about the degree and cortical topography of training-induced effects.

The previously reported training-induced changes in cortical excitability may also provide an important justification for the use of event-related NMES in neurorehabilitation. NMES, administered when the stimulated muscle was at rest, has been demonstrated to induce changes in cortical excitability through sensory afferent stimulation (Hamdy et al., 1998a; Ridding et al., 2000). One would expect that changes in cortical excitability might be even larger when excitatory effects of peripheral sensory stimulation and those of voluntary exercise cumulate at a cortical level. Indeed, studies have shown that NMES administered immediately prior to voluntary motor training increases the excitatory effects induced by the exercise (Sawaki, Wu, Kaelin-Lang & Cohen, 2006). This phenomenon has also been linked to enhanced functional recovery in patients with chronic stroke (Buetefisch & Cohen, 2008).

4.5: Motor Evoked Potentials in Corticobulbar Muscles

First to report on MEPs recorded from cranial muscles were Benecke, Meyer, Schoenle and Conrad (1988) who documented that MEPs could be evoked in

contra- and ipsi-lateral masseter, mentalis and hypoglossus muscles when TMS was performed with a round coil positioned over the lateral motor cortex. Optimal stimulation sites were reported to be between 2 and 4 cm lateral to the vertex, as in this position the outer circumference of the coil, known to induce maximal currents, was approximately 6 to 8 cm lateral to the vertex. Contralateral MEP onset latencies were reported to be 10.5 ms (SD 1.5 ms) for the masseter muscle, 12.0 ms (SD 1.3 ms) for the mentalis muscle and 11.8 ms (SD 1.8 ms) for the hypoglossus muscle. Pre-activation of these muscles was documented to reduce MEP onset latency by approximately 2.5 ms (SD 0.6 ms) and increase MEP amplitude. Further, MEP recordings were reported to be more stable during muscle pre-activation. For ipsilateral MEPs, onset latencies were substantially shortened and appeared at between 3.7 ms and 4.6 ms after the magnetic stimulus. This first investigation provided important baseline information about corticobulbar projections to the studies of facial muscles.

Subsequent research has most often evaluated MEPs recorded from the masseter muscle, a bilateral facial muscle responsible for jaw closure. Cruccu, Bernardelli, Inghilleri and Manfredi (1990) investigated MEPs, recorded from masseter and suprahyoid muscles in healthy individuals (N=25) and patients with hemiplegia following stroke (N=12) or trigeminal neuralgia (N=3), in response to TMS administered with a round coil over the vertex. For both muscle groups, pre-activation was found to be necessary in order to be able to record distinguishable MEPs. In fact, in the masseter muscle, MEPs could be recorded in only 4% of trials at rest, as opposed to 100% when the muscle was preactivated. In 7 of the 12 hemiplegic patients, no MEPs could be recorded from the affected, hemiplegic masseter muscle. In the healthy population, average onset latency of MEPs recorded from the masseter muscle was 5.9 ms (SD 0.4 ms) and average MEP amplitude was

2 mV (SD 0.6 mV). In a subgroup of 6 healthy individuals, MEPs were recorded from the suprahyoid muscles. Mean onset latency for these muscles was 6.9 ms (no SD reported) and mean amplitude was smaller than that reported for the masseter muscles (1 mV, no SD reported). The authors commented that when using surface electrodes, it was “impossible to differentiate between signals originating in the right and left muscles, or signals from the anterior digastric and mylohyoid muscles” (Cruccu et al., 1990, p. 1343). The reported values of onset latency and amplitude thus reflect a cumulative response of the suprahyoid muscle group, rather than of a specific muscle.

Macaluso, Pavesi, Bonanni, Mancina and Gennari (1990) have also investigated MEPs in the masseter muscle. The objective of their investigation was to determine the electrophysiological characteristics of the MEP response and a central conduction time for the masseter muscle. Onset latency and amplitude of MEPs were recorded from 10 healthy research participants in response to TMS over the motor cortex at rest and during approximately 20% of maximal contraction. Contralateral MEPs were reported to depend on pre-activation of the target muscle. Mean onset latency of masseter MEPs was 6.9 ms (SD 0.71 ms) when TMS was performed at maximal stimulator output. When stimulator output was decreased to 65% maximal output in 4 participants, MEP onset latency increased to 8.89 ms (SD 0.76 ms). In comparison to MEPs recorded from hand muscles, masseter MEPs were of lower amplitude, had a higher motor threshold and displayed a greater variability in both onset latency and amplitude within the recording session. The authors suggested that an unfavourable angle of the induced electric field and the stimulated neurons, or an overall smaller number of crossed connections originating from the masseter motor cortex, may be the underlying cause for these findings. The difference in onset latency, which was shorter than that documented by Benecke et

al. (1988) (10.5 ms), was attributed to lower TMS intensities used in the Macaluso study.

A creative approach was undertaken by McMillan et al. (1998a) to assure the reproducibility of MEPs recorded from the masseter muscle across several recording sessions. A modified, vacuum-formed plastic mask was used to position a 1-cm² grid system over the lateral scalp. The TMS coil was positioned over this grid at a tangent with a mechanical stereotactic system. Motor evoked potentials were recorded during 10% maximal voluntary contraction achieved during jaw clenching which was aided by visual sEMG biofeedback. Latency, amplitude and the area over which masseter MEPs could be evoked were recorded at the beginning, after the mask had been removed, and again after both the mask and the sEMG recording electrodes had been removed. A mean MEP onset latency of 8.9 ms (SEM 0.07 ms), a mean MEP amplitude of 25.8 μ V (SEM 0.77 μ V) and a mean response area of 5.4 cm² (SEM 0.6 cm²) were reported. Significant variations of each of the measures were documented between participants. After removal of the mask, MEP onset latency and amplitude did not change significantly. The response area data varied from pre-removal data, however, variance component analysis determined that most variance (75%) originated from biological noise, rather than removal of the mask (22%). In summary, the authors concluded that using the modified vacuum mask, robust masseter MEP responses could be recorded across different experimental sessions. Future research is needed to establish whether the described mask-design produces significantly superior results to those established in investigations using other coil positioning procedures, such as manual coil positioning over a grid marked on the scalp

Inter-session variability was investigated in more detail in a subsequent investigation of the same research group, by evaluating cross-session reliability of

the cortical topography of the masseter muscle, determined by parameters of the masseter cortical response map, including area, volume and height (McMillan, Watson and Walshaw, 1998b). Seven healthy research participants provided data for this investigation across two sessions. As in the previous study (McMillan et al., 1998a), masseter MEPs were recorded during muscle pre-activation achieved by jaw clenching. Mean onset latency of MEPs was 8.9 ms (SEM 0.04 ms) and did not differ between sessions. Highest MEP amplitude responses were located in the same map area in both sessions, although no absolute amplitude values were reported. Total response map area, volume and average height were highly reproducible across sessions (intra-individual coefficients of variability were 89%, 96% and 89%, respectively). In agreement with previous research that reported discrete motor maps for the limb, neck and tongue muscles on the precentral gyrus, the masseter muscle was discretely represented on the lateral motor strip. Further, significant inter-subject variability of the location of the masseter motor map was reported, which is in agreement with prior research on variations of discrete motor maps of human limb or pharyngeal musculature (Mortifee, Stewaert, Schulzer & Eisen, 1994; Hamdy et al., 1996).

A further study by McMillan, Graven-Nielsen, Romaniello and Svensson (2001) evaluated the effects of isometric and dynamic muscle contraction on MEPs recorded in the masseter muscle. Motor evoked potentials were recorded from 10 healthy research participants under three conditions of muscle contraction: isometric contraction at 10%, 20%, 30%, 40% and 50% of maximal contraction, and dynamic muscle contraction during jaw opening and intermittent jaw-muscle contraction during light to heavy tooth contact. For isometric contraction, a clear relationship between the degree of muscle contraction and MEP amplitude was observed. No effects on MEP amplitude were observed during the dynamic contraction conditions;

however, only 6 of the 10 participants displayed MEPs during this condition, therefore this observation needs to be interpreted with caution. Mean onset latencies of 8.0 ms (SEM = 0.1 ms) and 7.7 ms (SEM = 0.1 ms) were comparable for the isometric and dynamic conditions, respectively. As reported in previous research, MEPs could not be detected without muscle pre-activation.

In a recent clinical study, Gallas, Moiro, Debono, Navarre, Denis, Marie et al. (2007) reported that mylohyoid MEPs relate to swallowing function in chronic post stroke dysphagia. Sixteen individuals with chronic dysphagia and 8 individuals without swallowing impairment were examined. Ipsi- and contra-lateral MEPs to the site of TMS were recorded with surface electrodes from left and right mylohyoid muscles. In the non-dysphagic control group, mean MEP onset latency and amplitude were 6.9 ms (SEM 0.5 ms) and 460 μ V (SEM 70 μ V), respectively. In individuals with laryngeal penetration, ipsilateral MEPs showed increased onset latency [10.2 ms (SEM 3.5 ms)] when TMS was delivered over the affected hemisphere. In patients with aspiration, ipsilateral MEPs were smaller [96 μ V (SEM 68 μ V)] when TMS was delivered over the affected hemisphere. TMS over this hemisphere did not produce discernable, contralateral MEPs in 2 patients with pharyngeal residue and 3 patients with aspiration. Across patients, the amplitude of MEPs recorded from the side contralateral to the affected hemisphere was lower than in individuals without dysphagia. After TMS over the *unaffected* hemisphere, MEP onset latencies and amplitudes did not differ between the 3 participant groups. These results indicate that deterioration of swallowing function relates to changes in excitability of the cortical mylohyoid area. It is noteworthy that the authors specifically refer to the investigated muscles as the “mylohyoid” muscle. However, with the surface electrodes used in this investigation, it seems likely that the recorded sEMG signals represented not only mylohyoid muscle activity, but rather a

cumulative activation from the right and left submental muscles underlying the electrodes.

A relationship of cortical excitability and swallowing function has also been documented for the pharyngeal muscle representation on M1 (Fraser et al., 2002). Increased MEP amplitude after NMES of the pharyngeal musculature using facilitatory stimulus parameters was found to be related to a decrease in swallowing response time, pharyngeal transit time and aspiration severity in patients with dysphagia after acute stroke (time post onset 4 days). In contrast, Power et al. (2004) documented that NMES of the faucial pillars employing inhibitory stimulus parameters induced a decrease in MEP amplitude and that this change was related to a significant increase in swallowing response time. Both studies are reviewed in detail in Chapter 3.

Plowman-Prine, Triggs, Malcolm and Rosenbek (2008) evaluated the reliability of several measures of the suprahyoid and pharyngeal muscle cortical motor maps, including motor threshold, map area, map volume, maximal MEP site location and maximal MEP site size. Measures were recorded for both muscle groups across two sessions and intraclass correlation coefficients (ICC) were calculated. No exact measures of MEP onset latencies or amplitudes were reported. High reliability was found for most measures, including motor map area, lateral coordinate of maximal MEP size location, maximal MEP site size and motor threshold (ICCs varying between 0.76 and 0.98). Motor map volume and the antero-posterior coordinate of maximal MEP size location produced moderate reliability measures. These results support similar findings reported by McMillan et al. (1998b) for MEPs recorded from the masseter muscle. Both studies indicate that reliable measures of corticobulbar excitability can be obtained across multiple sessions from muscles innervated by the cranial nerves. This indicates the potential to detect

plastic changes in corticobulbar excitability, for example across the course of recovery or in response to treatment.

In summary, studies investigating corticobulbar excitability by means of MEPs have documented that: (1) approximate onset latency is 8 ms, with reports varying from 6.9 ms to 10.5 ms for different facial muscles; (2) pre-activation facilitates MEP amplitude and is necessary in some individuals to be able to detect MEPs or (3) if no pre-activation is present, MEPs are small and require high TMS intensities; (4) MEPs can be detected reliably across sessions; and (5) MEP amplitude of the pharyngeal and suprahyoid muscle groups is related to swallowing function.

Based on the literature review in this chapter, it is evident that the evaluation of MEP measures, specifically MEP amplitude and onset latency, can provide important information about the effects of rehabilitative treatment approaches on the excitability of corticobulbar projections. In the context of swallowing rehabilitation, evaluation of MEPs can provide important information about the central effects of NMES on the excitability of cortical projections to the muscles involved in swallowing. For the clinically readily accessible submental muscle group, this investigation is yet to be undertaken.

Additionally, MEPs reflect the degree of motor cortical excitability at the time of TMS discharge, allowing investigation of differences in cortical excitability across different tasks. Comparison of MEPs recorded during oral and pharyngeal swallowing-related muscle contractions will thus provide important insights into the relative contribution of the primary motor area to the motor control of these tasks. This investigation would be a valuable addition to fMRI data reported in previous publications. Before the results of such evaluations can be interpreted, the reliability

of task-related MEPs, that is, MEPs recorded in the functional context of muscle contraction or swallowing, needs to be established.

Statement of Current Questions

Data are emerging on the effects of NMES on swallowing neurophysiology. Previous research has provided evidence that effects are frequency-dependent, with the potential for excitatory or inhibitory changes to occur in the excitability of corticobulbar projections, as measured by MEP amplitude (Fraser et al., 2002; Power et al., 2004). Excitatory frequencies were found to differ as a function of muscle group; however, identification of optimal NMES frequencies for the submental muscle group, a site that is commonly targeted by NMES intervention in swallowing rehabilitation practices, has not been evaluated. Identifying both beneficial and potentially harmful stimulation frequencies is of primary importance in the development of NMES as a safe and effective rehabilitative treatment tool. Previous data have further indicated that other NMES parameters may influence the central effects induced by this modality, in particular the dose of the administered stimulation (Fraser et al., 2002) and the task context during which treatment is administered (DeKroon et al., 2005). The effects of these parameters have not been established for the submental muscle group.

MEPs have been widely used to quantify the excitability of corticospinal or corticobulbar projections. In swallowing rehabilitation, Fraser et al. (2002) and Power et al. (2004) have investigated MEPs recorded at rest to evaluate changes in corticobulbar excitability in response to NMES. The reliability of this measure is documented to be high when recorded from craniofacial muscles (Plowman-Prine et al., 2008). However, evaluation of the excitability of corticobulbar projections

during muscle pre-activation provides information about treatment-related changes in a functional context, thus increasing clinical relevance. No previous research has evaluated the effects of NMES of the muscles involved in swallowing on MEPs recorded in a task-related context. Further, the reliability of MEPs recorded in a functional context is not yet known.

It has been shown that repetitive performance of motor tasks affects cortical activation, particularly in the primary motor areas (Hauptmann, Skrotzki & Hummelsheim, 1997). It is therefore possible that repeated swallowing alone affects corticobulbar excitability. This would have important implications for the clinical application of NMES, and research is yet to identify whether changes in cortical excitability induced by NMES are superior to those induced by volitional swallowing exercises or repeated swallowing alone.

Finally, little is known about the precise role of cortical neural networks in the motor control of the pharyngeal phase of swallowing. The execution of the motor sequence is believed to be orchestrated by the closely linked interaction between the SMA, the NTS and switching neurons located in the nucleus ambiguus (NA) of the ventrolateral medulla (Miller, 1999; Jean, 2001). Research employing neuroimaging techniques has indicated that swallowing also activates multiple cortical regions, including the primary motor area (Martin et al., 2001; Martin, et al., 2004; Hamdy et al., 1999a; Toogood et al., 2005; Kern et al., 2001a). However, the limited temporal resolution of these technologies and potential methodological limitations of the paradigms used in previous studies make it difficult to clearly define the contribution of these regions to the complex swallowing motor plan. Cortical motor activation during muscle contraction affects MEP measures such as amplitude and onset latency. Evaluation of task-related MEPs recorded during various contraction conditions, including swallowing, may therefore provide

valuable information about the role of the primary motor area in the neural control of this phase of swallowing. No prior research has employed this methodology to address this question.

Chapter 5: Hypotheses

The primary aim of this research programme was to identify optimal NMES parameters for the submental muscle group. In a series of studies, two groups of healthy adult research participants underwent various event-related (Part V) or non-event-related (Part VI) NMES treatment protocols. Changes in corticobulbar excitability were measured across a 90 min post treatment period. Excitatory and inhibitory effects in response to NMES have been demonstrated previously across a similar timeframe (Fraser et al., 2002; Power et al., 2004).

A further aim was to investigate differences in corticobulbar excitability during three conditions of muscle activation: volitional contraction (VC), contraction during the pharyngeal phase of volitional swallowing (VPS, volitional pharyngeal swallowing) and contraction during the pharyngeal phase of reflexive swallowing (RPS, reflexive pharyngeal swallowing) (Part IV). All investigations were preceded by two pilot studies to establish the reliability of task-related MEPs as an outcome measurement, and to evaluate the effects of repeated volitional swallowing and time on MEP amplitude and onset latency (Part III). Refer to Figure 13 (pg. 127) for an overview of these studies.

The following hypotheses were tested. Each chapter contained within Parts III to VI provides an abbreviated introduction, which leads to one or more of these hypotheses.

5.1: Inter- and Intra-session and Inter- and Intra-rater Reliability

Background: Several sources of variance, for example the variability in participants' performance within and across sessions and the variability in identifying measures within and between investigators, may influence the reliability of data analyses. As no previous research has investigated reliability measures of submental MEPs, analyses determining inter- and intra-session and inter- and intra-rater reliability are required for the data collected in this research programme.

Hypothesis 1: Motor evoked potential amplitude and onset latency measures will be stable within one session and across multiple sessions, as indicated by high reliability measures. Further, inter- and intra-rater reliability measures will be high for both MEP amplitude and onset latency.

Justification: Previous research has established good reliability measures of MEP amplitude recorded from other facial muscle (McMillan et al., 1998b; Plowman-Prine et al., 2008) and similar measures are expected for submental MEPs.

Significance: Establishing reliability measures is an indication of the reproducibility of the data recorded in this research programme and an important prerequisite for the interpretation of these data. These analyses may also provide baseline measures for future investigations using the described methodologies.

Study design: For inter- and intra-session reliability, intra-class correlation coefficients (ICCs) of the data recorded from 10 participants during VC and VPS will be calculated across two and four sessions and across three blocks of five trials within one session. For inter-rater reliability, 20% of the data will be randomly selected and analysed by a trained research assistant, and will be compared to the data initially analysed by the principal investigator. For intra-session reliability, the principal investigator will re-analyse a separate, randomly selected 20% of the data.

The measures of the second analysis will be compared to those of the first analysis.

Intra-class correlation coefficients will be established for all reliability analyses.

5.2: The Effects of Repeated Volitional Swallowing on MEP Measures

Background: It has been shown that MEP amplitude increases in response to repetitive practice of novel motor tasks (Buetefisch & Cohen, 2008). For example, MEPs recorded from the extensor pollicis brevis muscle increase after a repeated thumb extension exercise. Interestingly, MEP amplitude increases associated with skill acquisition dissipate after the skill has been acquired or over-learned (Pascual-Leone, 1994; Muellbacher, 2002b). Fraser et al. (2003) documented that repeated water swallowing increases the excitability of cortical projections to the pharyngeal musculature. This change occurred immediately after task performance, but was not sustained at 30 min thereafter. In contrast, Thompson and Stein (2004) documented for the lower limb tibialis anterior and soleus muscles that 30 min of walking did not affect motor cortical excitability. It was therefore warranted to investigate whether repeated volitional swallowing affects cortical excitability across the timeframe employed in this research paradigm.

Hypothesis 2: Repeated volitional swallowing, performed 60 times at a rate of one swallow per approximately 12 s, will not increase corticobulbar excitability, as measured by increased MEP amplitude.

Justification: It may be argued that repeated volitional swallowing represents a volitionally initiated, but also reflexive motor task, similar to walking. As previous research has documented no effects of 30 min of walking on motor cortical excitability, similar results are expected for MEP recorded during the reflexive pharyngeal phase of volitional swallowing.

Significance: Identification of changes in corticobulbar excitability in response to repeated volitional swallowing is important, as they may exaggerate, or mask, effects induced by NMES.

Study design: Changes in MEP amplitude and latency recorded during VC and VPS will be evaluated at four assessments post treatment (5 min, 30 min, 60 min and 90 min). Averaged measures of change will be subjected to repeated measures analysis of variance (ANOVA) and the effects of “Assessment Time” will be calculated.

5.3: The Variability of MEPs Measures across Time

Background: Intra-individual variability in cortical excitability has been shown to follow a cyclic pattern, with substantial fluctuations in MEP amplitude observed over a period of seconds or minutes (Wassermann, 2008). Evaluation of MEP measures across the time frame employed in this research programme (90 min post treatment) may therefore be subject to intrinsic changes, which are unrelated to treatment effects. In contrast, the reliability of MEP measurements is documented to be high, indicating that averaging of multiple trials recorded over several seconds or even minutes minimises the effects of intrinsic variability (Plowman-Prine et al., 2008).

Hypothesis 3: Mean MEP amplitudes averaged across 15 trials will not vary significantly across a 2 hr period.

Justification: Changes in MEP parameters are measured across a 90 min period post treatment. Intrinsic fluctuations may affect treatment-induced changes in cortical excitability across time. The magnitude of this intra-individual variability therefore needs to be identified in order to be able to interpret the data recorded in this research programme.

Significance: This investigation will provide baseline data by identifying treatment unrelated fluctuations in MEP amplitude.

Study design: Changes in MEP amplitude and latency recorded during VC and VPS will be evaluated at four assessments post-treatment (5 min, 30 min, 60 min and 90 min). Averaged measures will be subjected to repeated measures ANOVA and the effects of “Assessment Time” will be calculated.

5.4: Comparison of MEP measures Recorded During Volitional Contraction, Pharyngeal Phase Swallowing and Reflexive Swallowing

Background: Swallowing is governed by swallowing pattern generators located in the brainstem (Jean, 2001). However, there is some indication that the primary motor cortex may also play a role in the motor control of swallowing (Kern et al., 2001b; Martin et al., 2004). While it has been previously documented that the primary motor cortex is activated during oral movements and volitional swallowing, it is not known to what extent this activation represents motor execution of pharyngeal muscles during the pharyngeal phase of swallowing. Previous data indicate that neural activity of the primary motor area may be smaller during volitional swallowing compared to voluntary tongue movements (Martin et al., 2004), or absent during the pharyngeal phase of volitional swallowing (Huckabee et al., 2003). Evaluation of MEPs recorded during VC, VPS and RPS provides insight into underlying differences in motor cortical activation.

Hypothesis 4: Submental MEPs recorded during muscle pre-activation will differ in amplitude between the three motor tasks (VC, VPS and RPS). Motor evoked potential amplitude will be larger during VC compared to MEP amplitudes recorded during the two swallowing conditions. Onset latencies of submental MEPs will not differ between conditions.

Justification: Volitional contraction requires substantial activation of the primary motor cortex and corticobulbar pathways, which will facilitate MEP amplitude to a larger degree than the swallowing conditions. These are believed to be mainly controlled by brainstem swallowing pattern generators. The speed of neural transmission, as measured by MEP onset latency, is not likely to differ between these tasks in healthy individuals, whose neural networks are functioning under optimal conditions.

Significance: This study investigates submental MEPs as a measure of corticobulbar excitability during three motor tasks. This investigation will provide insight into potential differences in the neural motor control of these tasks and may contribute to our understanding of the degree of activation of the primary motor area during the pharyngeal phase of volitional and reflexive swallowing. This study will further provide important baseline information for future evaluations of treatment effects on MEP amplitude and onset latency during swallowing.

Study design: Motor evoked potential amplitude and latency will be assessed during volitional contraction and the pharyngeal phase of volitional and reflexive swallowing. Mean amplitude and latency measures will be subjected to repeated measures ANOVA, paired-samples t-tests and chi square analyses.

5.5: The Effect of Stimulus Frequency on MEP Measures

Background: Previous research has documented changes in MEPs recorded from the musculature underlying the faucial pillars (Power et al., 2004) and pharyngeal mucosa (Fraser et al., 2002) in response to NMES. Changes in MEP amplitude were frequency-specific, with some frequencies facilitating and other frequencies inhibiting MEP amplitude. Differing excitatory frequencies were identified for the two muscle groups. This underscores the importance of identifying

optimal NMES parameters for the submental muscle group, which is often targeted by NMES intervention.

Hypothesis 5: Changes in MEP amplitude in response to NMES treatment will be frequency-dependent, with some frequencies facilitating and others inhibiting MEP amplitude. Motor evoked potential onset latencies are not expected to change.

Justification: In healthy individuals, NMES has been shown to affect corticobulbar excitability, reflected by MEP amplitude, and that changes were dependent on the frequency of the electrical stimulus (Fraser et al., 2002; Power et al., 2004). In these studies, the speed of neural conduction (MEP onset latency) was not affected by NMES.

Significance: This study will identify optimal NMES frequency for event-related NMES administered to the submental muscle group. This information may guide clinicians in their choice of treatment parameters for patients with dysphagia.

Study design: Changes in MEP amplitude and latency recorded during VC and VPS will be evaluated at four assessments post-treatment (5 min, 30 min, 60 min and 90 min). Averaged measures of changes will be subjected to repeated measures ANOVA and the effects of “Stimulation Frequency” and “Assessment Time” and the interaction between these variables will be calculated.

5.6: The Effect of Dose of NMES on MEP Measures

Background: Previous research has documented a relationship between the dose of NMES administered and the magnitude of change in corticobulbar MEP amplitude (Fraser et al., 2002). These researchers reported that maximal changes in MEP amplitude were observed after non-event-related NMES of 10 min duration, whereas non-event-related NMES of 5 min or 20 min duration produced smaller

post-treatment changes. It was therefore of interest to establish whether the effect found after 60 repetitions of 4 s swallowing-triggered stimulus trains was dependent on the number of stimulus train repetitions, or the duration of the stimulus train.

Hypothesis 6A: Sixty stimulus train repetitions will have a greater effect on MEP amplitude than 20 stimulus train repetitions.

Hypothesis 6B: Stimulus train of 4 s duration will have a greater effect on MEP amplitude than stimulus trains of 1 s duration.

Justification: A larger number of stimulus trains, or longer stimulus trains, provide an overall greater amount of sensorimotor stimulation to cortical sensory processing areas and motor excitation at the periphery, resulting in greater changes of corticobulbar motor excitation.

Significance: This study will identify whether the effects documented in the prior study (Chapter 10) can be achieved using fewer stimulus train repetitions or shorter stimulus trains. This may reduce treatment duration and facilitate transfer into clinical use.

Study design: Changes in MEP amplitude and latency recorded during VC and VPS will be evaluated at four assessments post-treatment (5 min, 30 min, 60 min and 90 min). Averaged measures of change will be subjected to repeated measures ANOVAs and the effects of “Dose” and “Assessment Time” and the interaction between these variables will be calculated, separately for each independent variable (number of repetitions and stimulus train duration).

5.7: Replication of Results Documented After 80 Hz NMES Protocol

Background: The studies presented in Part V have identified optimal stimulus parameters for event-related NMES of the submental muscle group. In order to establish whether these results can be replicated, NMES employing optimal

stimulus parameters and identical research procedures was administered to a second group of healthy adult participants.

Hypothesis 7: Similar effects as those documented previously (Chapter 10) will be observed in the second cohort undergoing event-related NMES at optimal stimulus parameters.

Justification: Replication of research findings is an important indication of the robustness of the effects documented in original research.

Significance: This comparison will identify the robustness of the research findings documented in the initial studies of this research programme.

Study design: Identical methods as employed for the identification of optimal stimulation frequency (as described in Chapter 10) will be used for this comparison. Changes in MEP amplitude and latency recorded during VC and VPS will be evaluated at four assessments post-treatment (5 min, 30 min, 60 min and 90 min) and compared to pre-treatment baseline using paired-samples t-tests.

5.8: The Effects of Non-event-related NMES

Background: Previous investigations undertaken in the framework of this research programme have established optimal NMES parameters for event-related NMES. The role of the task context during which NMES is administered remains unknown. Early evidence suggests that event-related NMES is more effective than non-event-related NMES (DeKroon, et al., 2005); however, no clear relationship has been established between the additional cognitive involvement required during event-related NMES and improved effectiveness of this treatment approach. Therefore, a comparison of the effects observed after event-related and non-event-related NMES was undertaken.

Hypothesis 8: Non-event-related NMES, administered at identical stimulus parameters as event-related NMES, will produce smaller changes in post-treatment outcome measures than event-related NMES.

Justification: Conceptually, it is plausible that time-locked endogenous and exogenous neuromuscular excitation may provide superior facilitation of the sensorimotor system than exogenous stimulation alone, as sensory and motor pathways are activated concomitantly. In fact, it has been shown that even traditional voluntary exercise of the biceps brachii muscle resulted in greater increase in muscle strength than non-event-related NMES (Holcomb et al., 2006).

Study design: Neuromuscular electrical stimulation employing optimal stimulus parameters (as described in Chapter 10) will be provided in a functional context (stimulation triggered by volitional swallowing) and at rest (stimulation triggered automatically). Changes in MEP amplitude and latency recorded during VC and VPS will be evaluated at four assessments post-treatment (5 min, 30 min, 60 min and 90 min). Averaged measures of change will be subjected to repeated measures ANOVA and the effects of “Event Context” and “Assessment Time” and the interaction between these variables will be calculated.

5.9: The Effects of 60 min Non-event-related NMES

Background: A number of clinical investigations have documented the effects of NMES in varying patient populations or healthy individuals. In the majority of these clinical studies, NMES was provided in a non-event-related context for 60 min per session (Freed et al., 2001; Suiter et al., 2006; Kiger et al., 2006). Outcome measures included swallowing efficiency and safety (Freed et al., 2001; Kiger et al., 2006) and measures of submental muscle activity (Suiter et al., 2006). It was therefore of interest to establish the effects of 60 min of non-event-

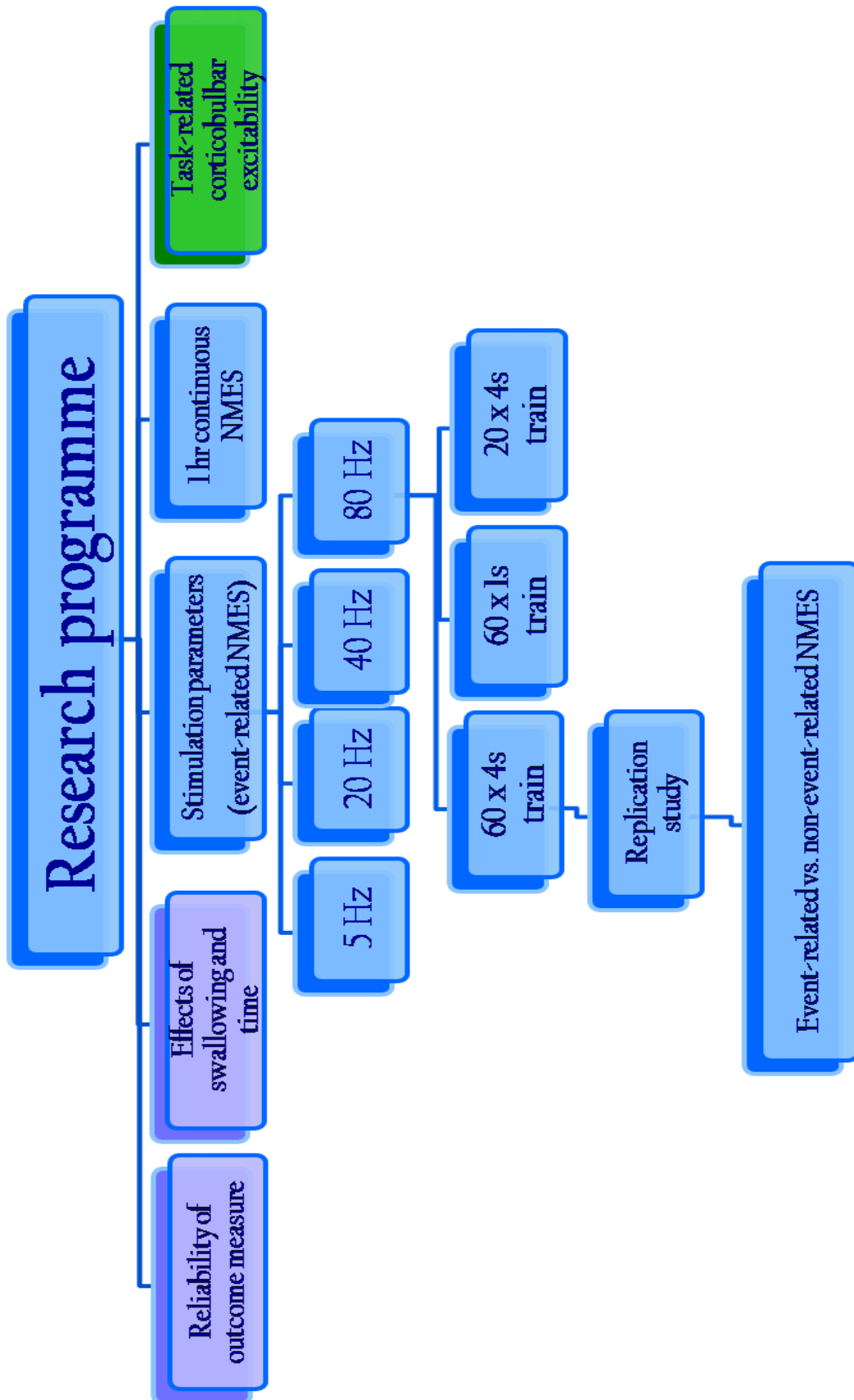
related NMES treatment on measures of the underlying neurophysiology of swallowing, specifically corticobulbar excitability.

Hypothesis 9: Sixty minutes of non-event-related NMES will produce increased MEP amplitude and no changes in onset latency. These changes will be greater than those administered during non-event-related NMES employing optimal NMES parameters.

Justification: Previous research has documented positive effects of 60 min non-event-related NMES treatment on a variety of post-treatment outcome measures. An increase in underlying corticobulbar excitability may account for these changes. These effects are expected to be larger than those observed after NMES employing optimal NMES parameters (section 5.8 above), because of the overall longer stimulation duration.

Study design: Non-event-related NMES will be provided for 60 min at the optimal stimulation frequency (as described in Chapter 10). Changes in MEP amplitude and latency recorded during VC and VPS will be evaluated at four assessments post-treatment (5 min, 30 min, 60 min and 90 min). Averaged measures will be subjected to repeated measures ANOVA and the effect of “Assessment Time” will be calculated.

Figure 13. Overview of research programme.



PART II

Chapter 6: Methodology

Part II of this thesis introduces the methodological design that was used in common for all individual studies undertaken in the framework of this programme. A description of the methods that are specific to each study, for example a description of research participants, treatment parameters and statistical analyses, will be provided in each of the various chapters.

6.1: Ethical Approval

All studies of this research programme were approved by the appropriate Health Ethics Committees. Approval for the initial pilot studies (Part III) was granted by the Upper South A Regional Ethics Committee, Ministry of Health, New Zealand. Approval for the event-related NMES study (Part V) was granted by the Upper South B Regional Ethics Committee, Ministry of Health, New Zealand. The non-event-related NMES study (Part VI) was approved by the Upper South A Regional Ethics Committee, Ministry of Health, New Zealand. All applications underwent appropriate Maori Consultation and were granted approval by a representative of Te Komiti Whakarite.

6.2: Materials

A novel data acquisition system designed for this programme consisted of a number of components, which as a whole allowed automatic elicitation and recording of MEPs during task-specific muscle contraction (Doeltgen, Ridding, Dalrymple-Alford & Huckabee, 2009). The individual components include

submental sEMG, a custom-built trigger system and a magnetic stimulator for focal stimulation of the motor cortex. Elicited MEPs were recorded using a computerised data acquisition system and data analysis was facilitated by custom-made analysis software.

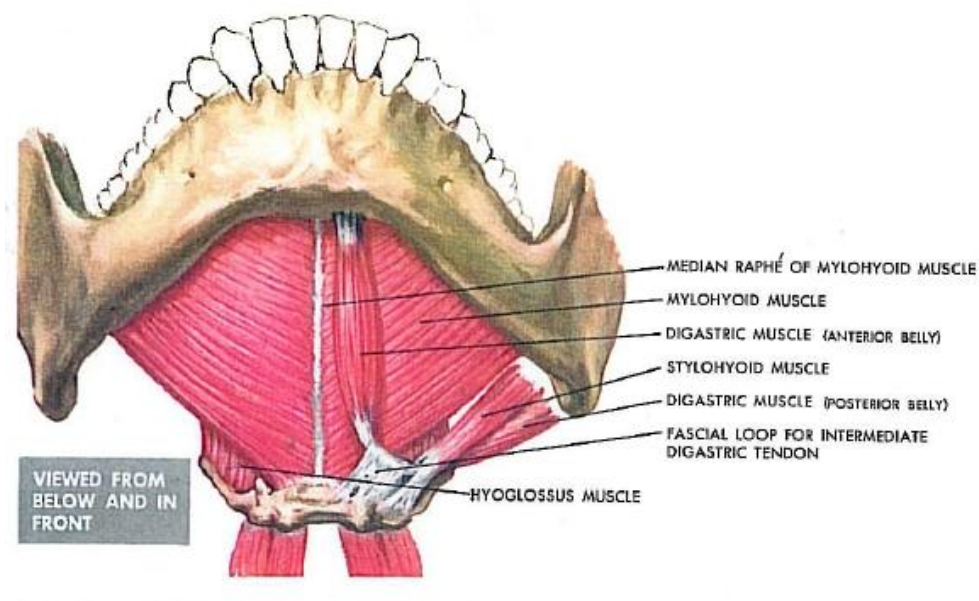
6.2.1: Muscles under investigation. Neuromuscular electrical stimulation was administered and outcome measures (MEPs) were recorded from surface electrodes positioned over the submental muscle group, which consists of the paired mylohyoid, geniohyoid and anterior belly of digastric muscles. Investigating the neurophysiology of the motor control of these muscles is of particular interest for several reasons. One, submental muscle activity represents a vital component of the pharyngeal phase of swallowing, in that it elevates and displaces the hyoid bone anteriorly. Because of ligament and muscle attachments to the thyroid and cricoid cartilages, this superior and anterior elevation of the hyoid bone consequently raises the larynx, which in turn aides airway protection and pulls open the relaxed upper oesophageal sphincter (Agur & Lee, 1999). Two, the submental muscle group is the target of a number of treatment approaches in dysphagia management [e.g., the headlift manoeuvre (Shaker, Kern, Bardan, Taylor, Stewart, Hoffmann et al., 1997), effortful swallow (Logemann, 1983) or electrical stimulation (Freed et al., 2001)] highlighting its importance in the execution of physiologic swallowing.

6.2.2: Submental surface electromyography and recording system. The area of skin to which the sEMG electrodes were to be attached was cleaned with an alcohol swab (Skin Cleansing Alcohol Prep, 6818-1, Webcol, Tyco Healthcare Group LP, Mansfield, MA) before small, self-adhesive gel electrodes (neonatal solid gel electrodes, BRS-50K, blue sensor) were mounted at midline over the submental

musculature in an anterior-posterior plane. With the surface electrodes used (2 cm long, extending 1 cm to either side of midline), this electrode placement recorded activity from the collective submental group: left and right digastric muscles (anterior belly), portions of the left and right mylohyoid muscles and left and right geniohyoid muscles (Figures 14 and 19). The intrinsic and extrinsic tongue muscles (e.g., the genioglossus muscles which lie just superior to the geniohyoid muscle) may have contributed to the measured sEMG signal. Participants were therefore asked to minimise tongue movement during data collection trials.

Figure 14.

Anterior hyo-mandibular musculature viewed from inferior. The “submental muscle group” consists of the mylohyoid muscle (depicted bilaterally), the digastric muscle (anterior belly) (depicted unilaterally) and geniohyoid muscle (not depicted, located superior to the mylohyoid muscle) (Netter, 2006).



All surface electrodes were connected to an EMG amplifier (Dual Bio Amp, ML 135, ADI Instruments) and recording system (Powerlab 8/30, ML 870, ADI Instruments). Muscle activity was monitored using the Scope software package, which is commercially available for use with the Powerlab system. Data were acquired at a rate of 10 kHz and high pass filtering of 10 Hz was employed. The trigger input channel of the recording system was connected to the trigger output channel of the magnetic stimulator, such that a sweep of 200 ms duration was recorded automatically when the magnetic stimulator was discharged. Each sweep recorded data 50 ms pre-trigger and 150 ms post-trigger. Data acquisition sweeps were triggered without delay and on the uprising slope of the transistor-transistor logic (TTL) trigger stimulus (Figure 15).

Figure 15.

Data acquisition system. Depicted are the EMG amplifier (Dual Bio Amp, ML 135, ADI Instruments, top device) and the data acquisition system (Powerlab 8/30, ML 870, ADI Instruments, bottom device).



6.2.3: Custom-built trigger system. A custom-built trigger system⁵

monitored the continuous sEMG signal transmitted from the amplifier (BioAmp) to the data recording system (Powerlab). The trigger device produced a single TTL impulse when the monitored sEMG signal breached a pre-set trigger threshold. This threshold was adjusted for each individual and for each session and represented 75% of the individual's mean sEMG peak amplitude of 10 volitional, noneffortful saliva swallows. Subsequent to production of a TTL impulse, the trigger device automatically disabled the production of a further trigger for 10 s to avoid unintentional recording of a stimulus that was not task-related. The 10 s offline phase was indicated by a small, orange light, which switched off when the system was again susceptible to triggering. The trigger device was connected via its output channel to the input channels of the magnetic stimulator and the electrical stimulator, depending on the research method employed at the time. During MEP data collection, the electrical stimulator was switched off, whereas the magnetic stimulator was switched off during the NMES treatment (Figure 16).

6.2.4: Electrical stimulator. A custom-built electrical stimulator was connected to the output channel of the triggering system. Upon detection of a TTL impulse, received from the trigger system, the stimulator produced an electrical current of pre-defined frequency, intensity and duration. The electrical current (200 μ s square pulses) was delivered to the participant through the gel electrodes mounted over the submental musculature (see Figure 19 for electrode placement, p. 143). The intensity of stimulation ranged from 0 mA to 25 mA. Pulses were generated at a frequency of 1.25 Hz, 2.5 Hz, 5 Hz, 10 Hz, 20 Hz, 40 Hz, or 80 Hz.

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

Stimulus duration could be set to 125 ms, 250 ms, 500 ms, 1000 ms, 2000 ms or 4000 ms (Figure 16 and Appendix 1).

Figure 16.

Trigger system (left) and electrical stimulator (right). The trigger system monitors the sEMG signal recorded by the Powerlab device (Figure 15), with the trigger threshold being adjustable to the predetermined sEMG value (refer to section 6.3.4). The three dials of the electrical stimulator allow adjustment of stimulus train duration (1st dial from left), stimulus frequency (2nd dial) and stimulus intensity (3rd dial). Note the orange light (middle) on the right, indicating the mandatory rest period during event-related NMES treatment trials. The green light (top) and yellow light (bottom) indicate device power and output of electrical current, respectively.



6.2.5: Magnetic stimulator. Focal transcranial stimulation was administered using a commercially available magnetic stimulator (Magstim 200², Magstim Company Limited, Whitland, Wales). A figure-of-8 coil with an outer wing diameter of 70 mm and a maximum output of 2.2 Tesla was used (2nd Generation Double 70mm Coil, 3190-00, Magstim Company Ltd, Whitland, Wales) (Figure 17).

Figure 17.

Magnetic stimulator (Magstim 200², Magstim Company Limited, Whitland, Wales) and figure-of-8 stimulation coil (2nd Generation Double 70mm Coil, 3190-00, Magstim Company Ltd, Whitland, Wales).



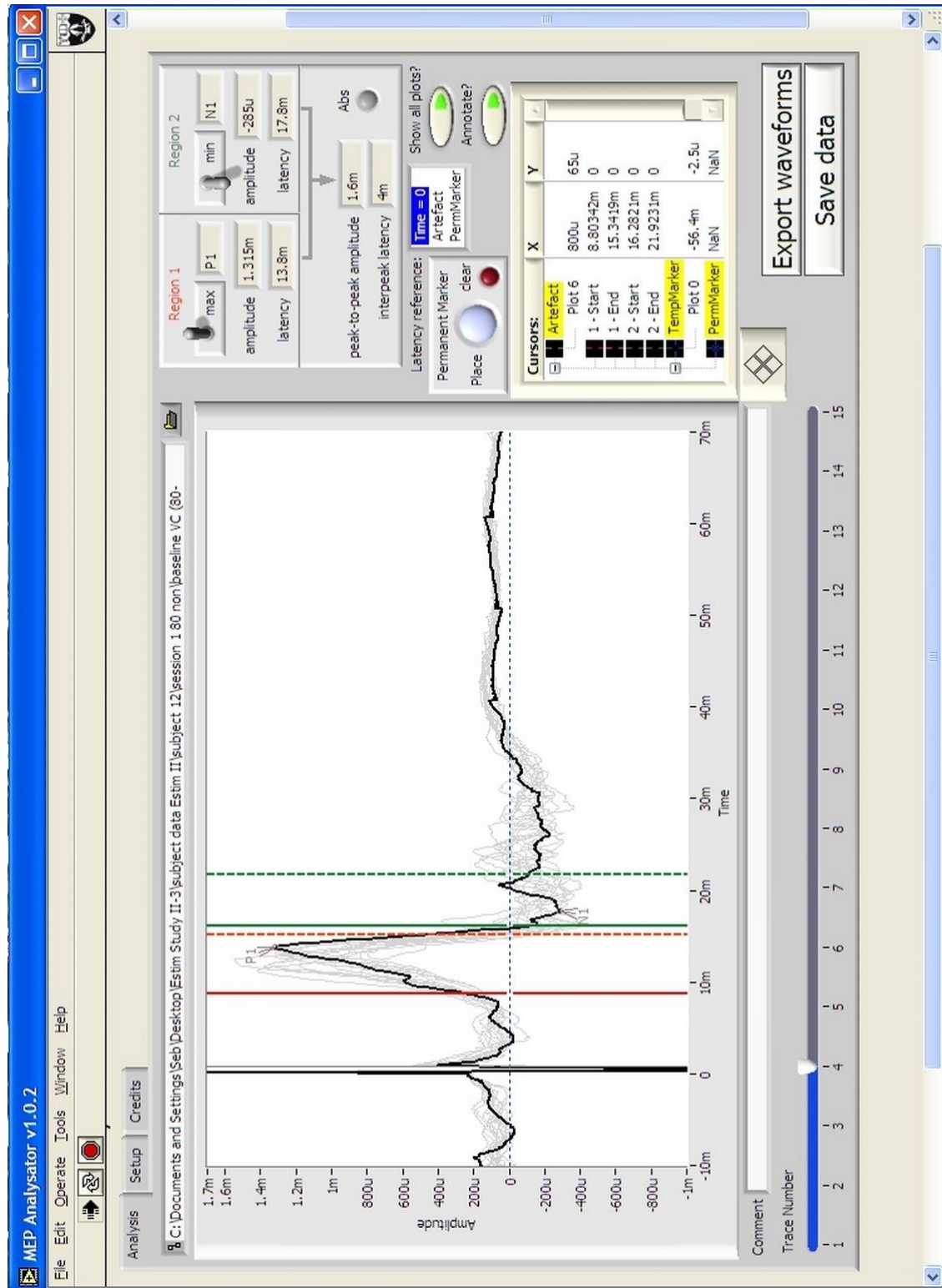
6.2.6: Analysis software. A custom-designed software package⁶ assisted in the detection of MEP peaks (first positive peak, P1 and first negative peak, N1). Data recorded initially as Scope files were saved as text files and opened in the MEP Analysator software (Figure 18). This programme allows definition of areas of interest, within which it will detect the most positive or most negative value. The selected data points are automatically labelled and transferred into a Microsoft Excel data sheet. In addition, all MEP waveforms measures were verified by manual checking offline.

⁶ MEP Analysator, G.A. O’Beirne, University of Canterbury, Christchurch, New Zealand, 2007

6.2.7: Definition of neuromuscular electrical stimulation (NMES). The term NMES is used as a general term to describe the application of electrical current to human nerve and muscle tissue. To differentiate between the specific types of NMES provided in this research programme, two descriptors define the broader acronym NMES. One, *event-related* neuromuscular electrical stimulation (event-related NMES) describes the provision of electrical current in the functional context of volitional swallowing, that is, each stimulation is triggered from sEMG activity recorded during a volitional swallow. Two, *non-event-related* neuromuscular electrical stimulation (non-event-related NMES) describes the provision of electrical current when the stimulated muscles are at rest. Both types are provided transcutaneously using surface electrodes.

Figure 18.

Data analysis software “MEP Analysator”. MEP waveform plots are displayed superimposed, with two regions of interest (red: first positive peak P1; green: first negative peak, N1) marked for identification of MEP amplitude.



6.3: Pre treatment Procedures

6.3.1: Participants. Participants were recruited from the public through advertisements (see Appendix 2). Participants contacted the principal investigator and were provided with information sheets prior to inclusion into the study. If participants agreed to participate in the study after reading the information sheet, they attended their first appointment at the laboratory. The principal investigator explained the study, equipment and procedures to the participants and answered any questions. Participants expressed full understanding of the procedures before agreeing to participate. Participants then signed consent forms and filled in three additional forms, including the Transcranial Magnetic Stimulation Safety Screen (TASS) (Keel et al., 2000) (see Appendix 3), the Edinburgh Handedness Inventory (Oldfield, 1971) (see Appendix 4) and a brief questionnaire about their past medical history and ethnicity (see Appendix 5).

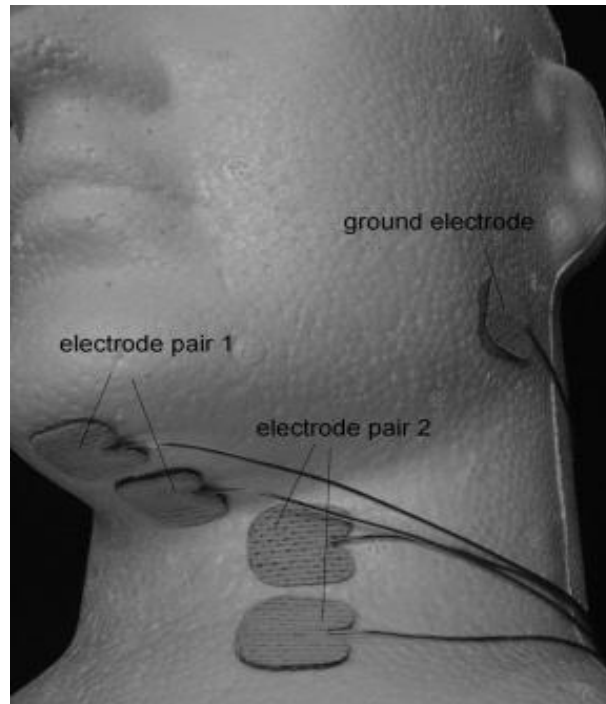
6.3.2: Electrode placement. Prior to commencement of data collection, participants were connected to the data acquisition system (see detailed description of components above). The skin of the cheek, chin and neck were cleaned with an alcohol swab before three or five surface electrodes, depending on study protocol, were adhered. One pair of electrodes was placed at midline under the chin over the submental muscle group. Electrode placement was standardised by placing the anterior electrode first, with its anterior edge located directly behind the bony edge of the mandible and the lateral edges overlapping 1 cm to either side of midline. The second electrode was placed posterior to the first electrode with a gap of 5 mm in between electrodes.

If required for the study protocol, a second pair of electrodes was positioned over the strap muscles of the neck, with the upper most electrode positioned approximately 2 cm lateral to midline over the upper edge of the thyroid cartilage and the lower electrode positioned approximately 1 cm below the upper electrode. A reference electrode was mounted over the bony mandibular prominence at the base of the vertical ramus. The two electrodes recording activity from the submental musculature were used during MEP measurement and NMES treatment. Electrodes mounted over the unilateral thyrohyoid musculature were used to trigger NMES during the event-related treatment sessions. Preliminary investigations of the delay between the onset of submental sEMG activity and the onset of sEMG activity in the thyrohyoid muscle revealed a relatively short delay in the order of 50-100 ms. A similar delay (56 ms between onsets of mylohyoid and thyrohyoid muscles) has been reported previously in dogs (Basmajian & DeLuca, 1985) and pigs (50 ms) (Thexton, Crompton & German, 2007). Burnett et al. (2005) documented that the onset of laryngeal elevation was more closely related to the onset of thyrohyoid activity than to the onset of mylohyoid activity. Therefore, triggering NMES from thyrohyoid activity assured that NMES occurred in the functional context of laryngeal elevation during the pharyngeal phase of the swallow.

The positively charged electrode (cathode) was placed over the anterior part of the musculature, just behind the mandible, whereas the negative electrode (anode) was placed just anterior to the hyoid bone with a space of approximately 5 mm between the electrodes. Electrical current flow was therefore in the anterior-posterior direction (cathode to anode). Refer to Figure 19 for electrode placements. Several baseline measures were then recorded from each participant.

Figure 19.

Placement of surface electrodes over the midline raphe of the submental muscle group (electrode pair 1), unilateral thyrohyoid musculature (electrode pair 2) and a ground electrode.



6.3.3: Practice of research tasks. Motor evoked potentials were triggered by and recorded during pre-activation of the submental musculature. Pre-activation was achieved during two muscle contraction conditions: volitional contraction (VC) and volitionally initiated pharyngeal swallowing (VPS, volitional pharyngeal swallowing). For volitional swallowing, participants were instructed to “swallow your saliva as you normally would”. However, participants were instructed to limit any volitional, oral preparatory movements, in particular tongue movements, during this task. For the volitional contraction task, participants were instructed to “contract the muscles under your chin as if stifling a yawn”. Visual feedback about the degree of muscle contraction was given to participants by means of online submental sEMG. Participants were asked to match the degree of muscle activity during volitional contraction to the degree of muscle contraction displayed during

swallowing. Participants practiced the contraction task, alternating between swallows and contractions, for approximately 5 min prior to data collection.

6.3.4: Trigger threshold. At the beginning of each session, the individual threshold used to trigger both magnetic stimulation (outcome measurement) and NMES (treatment) was identified. To determine trigger threshold for magnetic stimulation, each participant performed 10 noneffortful saliva swallows and the peak sEMG amplitude of each swallow was recorded at the submental muscle group and averaged. Seventy-five percent of this mean amplitude was set as the threshold at which the trigger system produced a TTL impulse, which subsequently triggered the magnetic stimulator. This value was chosen as it represents submental sEMG activity related to the pharyngeal phase of swallowing and rarely produced elicitation of a trigger impulse from sEMG activity during rest periods.

To determine trigger threshold for event-related NMES, the same procedure was undertaken for the electrodes mounted over the thyrohyoid muscles. Trigger thresholds were identified for each participant at the beginning of each session as minor changes in electrode placement between sessions may affect impedance, that is, sEMG signal amplitude.

6.3.5: Identification of optimal scalp location. The optimal scalp location over which largest MEP amplitudes could be elicited was identified in the following manner. First, the vertex was identified according to the international 10-20 electrode system (Jasper, 1958). Starting over the left hemisphere, an area approximately 4 cm anterior and 8-10 cm lateral was then searched for the optimal scalp location at 60% maximal stimulator output. Participants volitionally contracted their muscles, as practiced in the training module, any time after the orange light of

the trigger device had switched off, indicating that the 10 s offline period was over. The trigger system activated the magnetic stimulator when the pre-set trigger threshold was breached. If no MEPs could be detected at 60% maximal stimulator output, stimulation intensity was increased in 10% increments until MEPs were detected or maximal stimulator output was reached and the procedure was repeated at each intensity level. Subsequent to identification of the optimal stimulation site, maximal MEP amplitude was established at this site by increasing magnetic stimulation intensities until no increase in MEP amplitude was observed or maximal stimulator output was reached. The same procedures were then undertaken over the right hemisphere. Data collection was performed over the hemisphere that produced greatest MEPs. TMS intensity for further MEP testing was set to the value at which 50% of the maximal MEP amplitude was recorded.

6.3.6: *Electrical stimulus intensity.* Before commencement of data collection, the intensity level for NMES treatment was identified for each participant. A continuous electrical current was delivered through the surface electrodes adhered to the submental muscle group. Stimulation intensity commenced at 1 mA and was increased in 3 mA increments until the participant reported a painful sensation and that a further increase in stimulus intensity could not be well tolerated. Each level of intensity was provided for at least 10 s to allow the participant to accommodate to each level of stimulation. Intensity for subsequent NMES treatment protocols was set to 75% of the individual's pain threshold. As with the sEMG trigger threshold, the NMES threshold was identified at the beginning of each session to compensate for slight differences in electrode placement between sessions. This level of intensity was chosen based on earlier findings by Fraser et al. (2002) who documented that the size of the effect induced

by non-event-related NMES was directly related to the intensity of the electrical stimulus with statistically significant effects only observed at the highest investigated intensity (75% of maximal tolerated intensity)⁷.

6.4: Data Collection Procedures

Motor evoked potential measures were recorded before and after NMES treatment in order to identify changes in motor cortical excitability. After all pre treatment preparations were completed, 15 MEPs were recorded during both the VC and VPS conditions as baseline measures. The submental surface electrodes were then connected to the electrical stimulator and the thyrohyoid muscle electrodes were connected to the trigger device (if NMES was to be event-related). Neuromuscular electrical stimulation treatment was provided using the stimulation parameters described in detail in later chapters.

After the treatment period was completed, 15 MEPs were recorded immediately, that is within 5 min after completion of the NMES treatment⁸, and at 30 min, 60 min and 90 min post treatment during both the VC and VPS contraction conditions. Similar intervals of post treatment outcome measurement were reported by Fraser et al. (2002) and Power et al. (2004) who documented that post treatment effects on MEP amplitude in response to NMES evolved over a 60-min period. At the end of each data collection session, electrodes were removed from the participant and any pen markings on the scalp were removed with an alcohol swap. Participants were asked to report any adverse side effects and the next appointment was scheduled.

⁷ On the background of the considerations outlined in Chapter 3, the intensity of the NMES stimuli administered in this research programme provides combined sensory and motor stimulation, as identified by a “grabbing” sensation reported by participants. It will from hereon also be referred to as “sensorimotor” stimulation.

⁸ For ease of presentation and readability, this time point will be referred to as “5 min post treatment”.

6.5: Data Processing and Analysis

All MEP measures were recorded as Scope files (.sfwdat file) and text files (.txt file) in blocks of 15 trials according to contraction condition (VC, VPS or RPS) and time of recording (pre treatment or one of four post treatment recordings). After data collection for each session was completed, the text files were opened in the custom-designed analysis software and inspected visually by the principal investigator. Regions of interest were defined around the first positive peak (P1) and the first negative peak (N1) (Figure 18). The peaks of all trials were confirmed to be within the respective regions of interest before the computed values were labelled and exported automatically into a separate Microsoft Excel data sheet. P1-to-N1 amplitudes were also calculated automatically. The principal investigator then inspected each individual MEP trial and determined MEP onset latency by moving a cursor along the MEP trace to the point of estimated MEP onset. Motor evoked potential onset was defined as the first significant rise of P1 from baseline. The latency from time 0 s (coinciding with the trigger of the magnetic stimulator and the magnetic stimulation artefact) to the visually determined point of MEP onset was displayed by the MEP Analysator software and transferred into a separate Microsoft Excel data sheet by the investigator.

All blocks of 15 trials recorded pre and post treatment were subjected to repeated measures ANOVAs to identify potential trial effects. If there was no trial effect, the 15 individual values were collapsed to a single average value, which was used in subsequent statistical analyses. Inter- and intra-rater reliability and inter- and intra-session reliability were calculated subsequent to conclusion of all data collection (see Chapter 7). Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 15.0.0, September 2006). A p-value < 0.05 was accepted to determine statistical significance.

PART III

Chapter 7: Evaluation of MEP Reliability Measures⁹

Previous research has evaluated the reliability of MEP related measures recorded from a variety of muscle groups in different muscle contraction states. Christie, Fling, Crews, Mulwitz and Kamen (2007) established the reliability of mean MEP amplitude recorded from the relaxed abductor digiti minimi muscle within and across multiple sessions in healthy research participants. Intra-class correlation coefficients (ICCs) were established for averages calculated from different numbers of trials. Reliability was found to be high for intra-session comparisons (ICC = 0.9) if mean MEP values were calculated from a sufficiently large number of trials (five trials). Inter-session reliability established for mean MEP amplitudes averaged across five trials was also sufficiently high (0.82). Kamen (2004) tested the reliability of MEP amplitude recorded from the biceps and first dorsal interosseous muscles in young, healthy volunteers during rest and muscle contraction conditions. Reliability was assessed across three days for the mean MEP amplitude averaged across five trials. Intra-class correlation coefficients ranged from 0.6 to 0.8 for all muscle contraction conditions.

For the corticobulbar-controlled facial muscles, McMillan et al. (1998a) evaluated the reliability of MEP motor maps of the human masseter muscle at rest. Coefficients of reliability of total map area, volume and height were found to be $r = 0.89, 0.96$ and 0.89 , respectively. Recently, Plowman-Prine et al. (2008) evaluated reliability measures for mapping the swallowing musculature in the human motor

⁹ Data from this chapter have been published as:
Doeltgen, S. H., Ridding, M. C., O'Beirne, G. A., Dalrymple-Alford, J., & Huckabee, M. L. (2009). Test-retest reliability of motor evoked potentials (MEPs) at the submental muscle group during volitional swallowing. *Journal of Neuroscience Methods*, 178, 134- 137.

cortex at rest. For the suprahyoid musculature, this group documented moderate to good test-retest reliability (ICC) for motor map volume (0.70) and maximal MEP size location (0.97), as well as motor map area, maximal MEP site location (lateral coordinates: 0.97; anterior-posterior coordinates: 0.68; maximal MEP site size: 0.78 and motor threshold: 0.9, respectively). In summary, high reliability has been documented for MEP measures recorded from a variety of muscles, including some of the facial muscles. It is noteworthy that the experimental conditions under which MEP measures were acquired differed between investigations; therefore, the reported reliability measures can only be interpreted in the context of the methods used to establish them.

No previous research has evaluated reliability of MEP measures recorded from the submental muscle group during muscle pre-activation related to volitional contraction or volitional swallowing. As such, no reliability data exist for the methodology employed to acquire the MEP measures analysed in the current research programme. Therefore, ICC measures were calculated for MEP amplitude and onset latency measures within one and across multiple sessions. This analysis was modelled by the procedures published by Christie et al. (2007).

Additionally, inter-rater reliability was calculated for a randomly chosen 20% of the entire data set evaluated in this research programme, which was analysed by a second investigator. Intra-rater reliability was calculated for a different randomly chosen 20% of the data, which was re-analysed by the principal investigator and compared to the measures of the first analysis.

7.1: Methods Inter- and Intra-session Reliability

7.1.1: Participants. Ten young, healthy adults [mean age: 27.5 yrs; (SD 2.9 yrs), 7 females, 7 right-handed (Oldfield, 1971)] attended a total of four sessions.

Participants provided written informed consent and expressed full comprehension of the research procedures. Participants reported no medical history, current symptoms of dysphagia or neurological impairment and no drug use that would potentially affect their swallowing or neurological function.

7.1.2: Data recording. Data acquisition procedures and technical set up were described in Chapter 6. Two surface electrodes over the submental muscle group and the reference electrode mounted over the bony mandibular prominence at the base of the vertical ramus were used for this study. After the trigger threshold was determined and the optimal scalp location for eliciting MEPs was identified, 15 MEPs were recorded during both the VC and VPS contraction conditions. These measures were recorded for each participant during each of four independent sessions performed on separate days at approximately the same time of day.

For inter-rater reliability, both the principal investigator and the research assistant determined MEP amplitude and onset latency measures. Intra-class correlation coefficients were calculated using individual data points, not mean values. For intra-rater reliability, measures recorded by the principal investigator in the first analysis were compared to the measures identified in the second analysis and ICC values were calculated for these data.

7.1.3: Data preparation and analysis. To determine the intra-session reliability of MEP peak-to-peak amplitudes and onset latencies, the 15 trials of each contraction condition recorded in the first session were divided into three blocks of five trials each. Intra-class correlation coefficients were calculated for the mean values of these blocks of five trials. Additionally, ICCs were calculated for the mean

values of only the first three or first four trials of each block to determine which number of trials produced the greatest intra-session reliability.

To examine inter-session variability, a two-way repeated measures ANOVA was performed first to identify influences of block-within-session (15 trials divided into three blocks of five trials for each session), the four sessions and the interaction between these factors. Subsequently, inter-session reliability of both MEP measures was determined between Session 1 and each of the three subsequent sessions for each condition. Intra-class correlation coefficients were calculated for blocks of the first 5, 10 and all 15 trials in order to identify the number of trials that produced optimal inter-session reliability. Further, ICCs for inter-session reliability across all four sessions were calculated, again using blocks of the first 5, 10 and all 15 trials.

Inter- and intra-rater reliability measures were established for the all investigations undertaken in the framework of this research programme. Identification of data points and reliability analyses were performed after completion of the data collection phases for all studies.

For inter-rater reliability, a randomly chosen 20% of the data were analysed by a trained research assistant who was blind to the treatment condition. The research assistant was familiar with the area of research and had received training on analysis of MEP waveforms similar to, but independent from, the ones recorded for these studies.

The principal investigator re-analysed another randomly chosen 20% of the data several weeks after completion of the studies in order to establish intra-rater reliability. During this analysis, he was blinded to the treatment condition and time of data recording within each session.

7.2: Results Inter- and Intra-session Reliability

Two of the 10 participants did not display identifiable MEPs during the swallowing task and were therefore excluded from further analyses of the VPS condition data. In five of the remaining participants, MEPs were recorded from the left hemisphere. For the other three participants MEPs were recorded from the right hemisphere. Figure 20 represents typical MEP waveforms of one participant.

7.2.1: Intra-session reliability – MEP amplitude. Intra-class correlation coefficients for the three blocks of five trials recorded in the first session revealed high within-session reliability, ICC = 0.915 for VPS and 0.909 for VC. Decreasing the number of trials per block led to a progressively mild reduction in ICC measures in both conditions [(blocks of four: ICC = 0.888 (VPS), ICC = 0.895 (VC); blocks of three: ICC = 0.797 (VPS), ICC = 0.85 (VC)].

7.2.2: Intra-session reliability – MEP onset latency. Intra-class correlation coefficients for the three blocks of five trials recorded in the first session revealed high within-session reliability, ICC = 0.89 for VPS and 0.954 for VC. Decreasing the number of trials per block led to a progressively mild reduction in ICC measures in both conditions [(blocks of four: ICC = 0.884 (VPS), ICC = 0.946 (VC); blocks of three: ICC = 0.807 (VPS), ICC = 0.953 (VC)].

Figure 20a.

MEP waveforms of one representative research participant, recorded during the volitional contraction (VC) condition. Fifteen overlaid MEP traces are displayed, with one MEP waveform highlighted in bold. MEPs recorded during four independent sessions are presented.

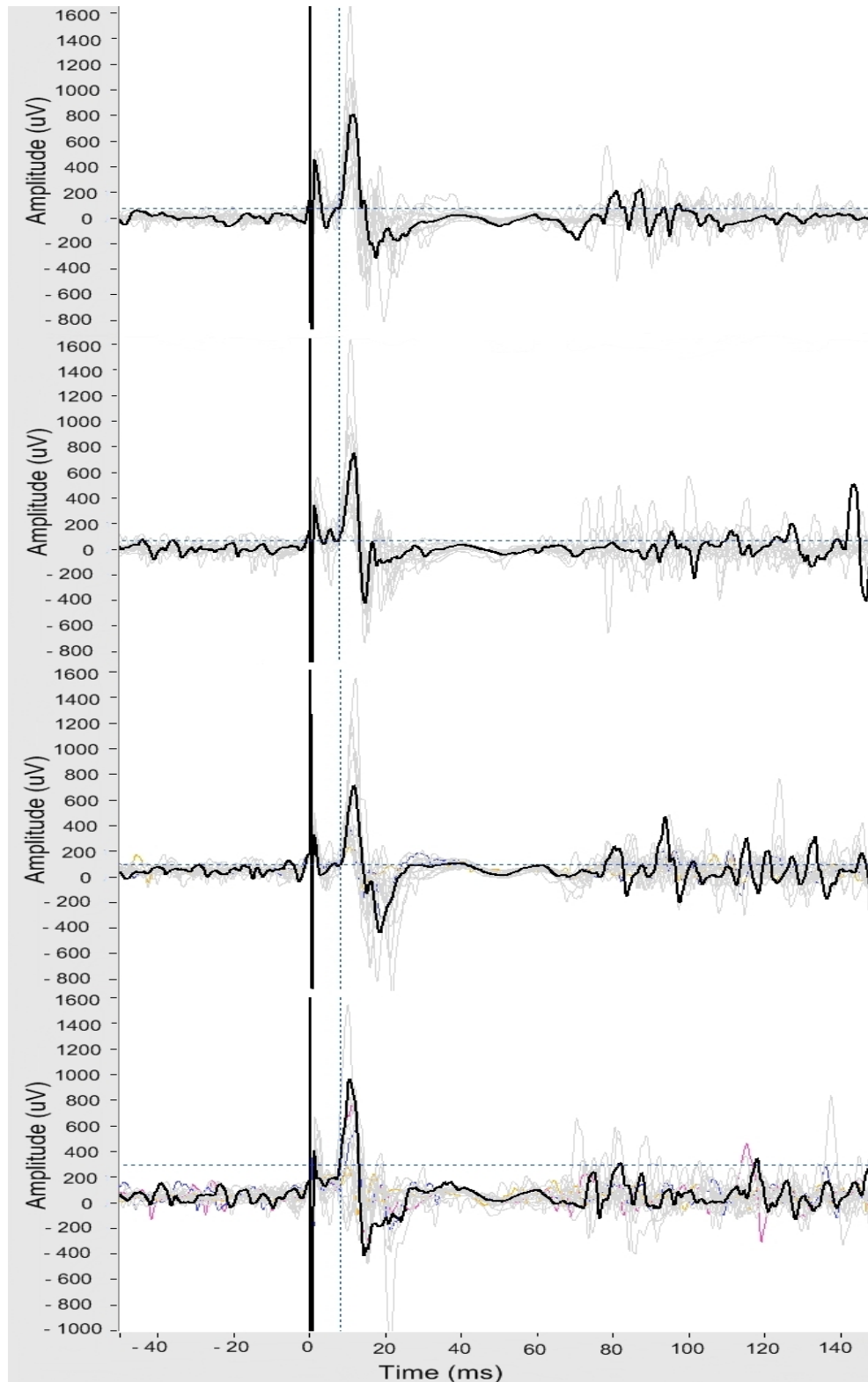
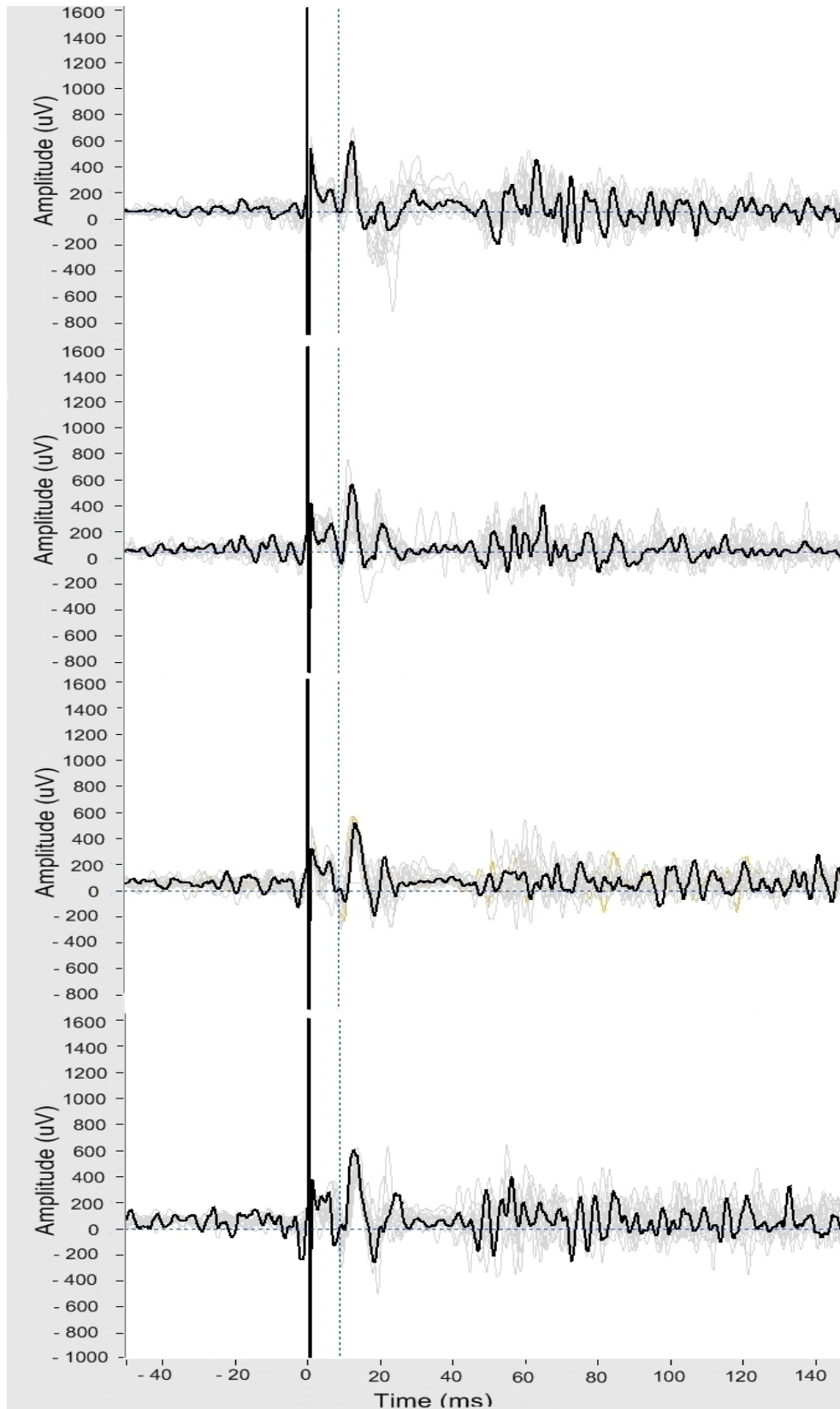


Figure 20b.

MEP waveforms of one representative participant, recorded during pharyngeal swallowing (VPS). Fifteen overlaid MEP traces are displayed, with one MEP waveform highlighted in bold. MEPs recorded during four independent sessions are presented.



7.2.3: Inter-session reliability – MEP amplitude. Two-way repeated measures ANOVA on the first, second and third blocks of five trials of each of the four sessions revealed no significant influence of block or session and no significant interaction between these factors (Table 1). MEP amplitudes for all blocks and sessions are presented in Table 2. As no changes in mean levels of performance were evident across blocks or sessions, ICCs will provide a robust estimate of inter-session reliability in the context of stable MEPs. Correlation coefficients for all comparisons are presented in Table 3. Inter-session reliability was calculated between session 1 and each of the subsequent three sessions, for blocks of the first 5, 10 and all 15 trials. ICC measures ranged from 0.486 [five trials per block (VPS)] to 0.909 [(10 trials per block (VPS))]. Interestingly, marginally higher ICCs were achieved for blocks of 10 trials in five out of six comparisons and for all four sessions combined.

Table 1.

Differences in mean MEP amplitude across blocks (within session comparisons) and sessions.

Condition	Block	Session	Interaction
VPS - amplitude	$F_{[2,14]} = 1.0, p = 0.4$	$F_{[3,21]} = 1.0, p = 0.8$	$F_{[6,42]} = 1.8, p = 0.12$
VC – amplitude	$F_{[2,18]} = 0.12, p = 0.89$	$F_{[3,27]} = 1.0, p = 0.4$	$F_{[6,54]} = 1.1, p = 0.11$
VPS – latency	$F_{[2,14]} = 0.41, p = 0.96$	$F_{[3,21]} = 0.92, p = 0.45$	$F_{[6,42]} = 1.35, p = 0.25$
VC – latency	$F_{[2,18]} = 0.39, p = 0.69$	$F_{[3,27]} = 0.22, p = 0.88$	$F_{[6,54]} = 0.52, p = 0.79$

Table 2.

Mean and SD of MEP amplitude (in μV) across blocks and sessions.

	Session 1		Session 2		Session 3		Session 4	
	VPS	VC	VPS	VC	VPS	VC	VPS	VC
1 st block	511.41 (226.12)	725.9 (427.16)	541.36 (278.38)	844.1 (433.7)	603.24 (228.82)	788.8 (444.8)	605.82 (339.69)	717.95 (359.85)
2 nd block	572.15 (290.67)	737.7 (426.9)	520.98 (148.37)	849.5 (466.4)	512.28 (198.18)	835.1 (430.4)	555.41 (229.44)	708.9 (321.1)
3 rd block	585.1 (313.86)	731.2 (365.2)	494.2 (178.16)	933.5 (484.75)	496.89 (170.95)	740.5 (401.3)	585.24 (299.4)	673.8 (308.7)
Mean	556.1 (271.3)	731.43 (394.9)	518.7 (195.6)	874.5 (450.7)	537.4 (190.2)	788.1 (407.7)	582.7 (282.7)	700.1 (315.8)

Table 3.

Inter-session reliability of MEP amplitude between Session 1 and each of three subsequent sessions and across all four sessions. ICCs are presented for two conditions, volitional muscle contraction (VC) and volitional pharyngeal swallowing (VPS), for blocks of 5, 10 and 15 trials.

Session	VC				VPS			
	1 & 2	1 & 3	1 & 4	All	1 & 2	1 & 3	1 & 4	All
15 trials	0.829	0.542	0.690	0.639	0.553	0.811	0.642	0.690
10 trials	0.874	0.615	0.700	0.688	0.609	0.909	0.649	0.716
5 trials	0.842	0.586	0.629	0.639	0.641	0.887	0.486	0.657

Note. Largest ICC values of each comparison are displayed in bold.

7.2.4: Inter-session reliability – MEP onset latency. Repeated measures

ANOVA on the first, second and third blocks of five trials of each of the four sessions revealed no significant influence of block or session and no significant interaction between these factors (Table 1). MEP onset latencies for all blocks and sessions are presented in Table 4. As no changes in onset latencies were evident across blocks or sessions, ICCs will provide a robust estimate of inter-session reliability in the context of stable MEPs. ICCs for all comparisons are presented in Table 5. Inter-session reliability was calculated between Session 1 and each of the subsequent three sessions, for blocks of the first 5, 10 and all 15 trials. ICC measures ranged from 0.706 [five trials per block (VPS)] to 0.963 [(15 trials per block (VC))]. Highest ICCs were achieved for blocks of 15 trials for all comparisons.

Table 4.

Mean and SD of MEP onset latency (in ms) across blocks and sessions.

	Session 1		Session 2		Session 3		Session 4	
	VPS	VC	VPS	VC	VPS	VC	VPS	VC
1 st block	9.3 (1.7)	8.8 (1.5)	9.2 (1.4)	8.8 (1.5)	9.5 (1.6)	8.8 (1.3)	8.6 (1.4)	8.5 (1.6)
2 nd block	9.2 (1.5)	8.9 (1.5)	9.1 (1.7)	8.8 (1.5)	9.4 (1.7)	8.8 (1.5)	8.9 (1.5)	8.6 (1.6)
3 rd block	8.9 (1.7)	8.7 (1.4)	9.2 (1.7)	8.7 (1.5)	9.4 (1.5)	8.9 (1.4)	9.3 (1.7)	8.9 (1.3)
Mean	9.1 (1.6)	8.8 (1.4)	9.2 (1.5)	8.8 (1.4)	9.4 (1.6)	8.8 (1.3)	8.9 (1.5)	8.7 (1.5)

Table 5.

Inter-session reliability of MEP onset latency between Session 1 and each of three subsequent sessions and across all four sessions. ICCs are presented for two conditions, volitional muscle contraction (VC) and volitional pharyngeal swallowing (VPS), for blocks of 5, 10 and 15 trials.

Intraclass correlation coefficients MEP onset latency								
	VC				VPS			
Session	1 + 2	1 + 3	1 + 4	All	1 + 2	1 + 3	1 + 4	all
15 trials	0.963	0.940	0.873	0.909	0.883	0.895	0.770	0.860
10 trials	0.932	0.913	0.813	0.872	0.806	0.856	0.764	0.821
5 trials	0.953	0.800	0.721	0.759	0.787	0.831	0.706	0.744

Note. Largest ICC values of each comparison are displayed in bold.

7.3: Results Inter- and Intra-rater Reliability

7.3.1: Inter-rater reliability. Table 6 summarises ICC values for all comparisons. Reliability of MEP amplitude measures was consistently high (ICC > 0.858) whereas reliability measures for MEP onset latency were slightly lower (ICC > 0.672).

7.3.2 Intra-rater reliability. Intra-rater reliability coefficients were consistently high for both MEP amplitude (ICC > 0.967) and onset latency measures (ICC > 0.753) (Table 7).

Table 6.

Inter-rater reliability (ICCs) of MEP amplitude and onset latency measures across all investigations.

Investigation		VC		VPS
Inter-/ intra-session reliability investigation	Amplitude	0.99	Amplitude	0.967
	Latency	0.672	Latency	0.696
Frequency effect investigation	Amplitude	0.997	Amplitude	0.925
	Latency	0.917	Latency	0.719
Dose effect investigation	Amplitude	0.996	Amplitude	0.957
	Latency	0.703	Latency	0.823
80 Hz NMES replication	Amplitude	0.976	Amplitude	0.868
	Latency	0.727	Latency	0.797
Non-event-related NMES investigation	Amplitude	0.988	Amplitude	0.858
	Latency	0.731	Latency	0.714
Continuous NMES investigation	Amplitude	0.962	Amplitude	0.996
	Latency	0.834	Latency	0.883

Table 7.

Intra-rater reliability (ICC) of MEP amplitude and onset latency measures across all investigations.

Investigation		VC		VPS
Inter-/ intra-session reliability investigation	Amplitude	0.994	Amplitude	0.993
	Latency	0.811	Latency	0.868
Frequency effect investigation	Amplitude	0.995	Amplitude	0.988
	Latency	0.903	Latency	0.903
Dose effect investigation	Amplitude	0.997	Amplitude	0.995
	Latency	0.904	Latency	0.897
80 Hz NMES replication	Amplitude	0.992	Amplitude	0.974
	Latency	0.905	Latency	0.892
Non-event-related NMES investigation	Amplitude	0.990	Amplitude	0.967
	Latency	0.791	Latency	0.809
Continuous NMES investigation	Amplitude	0.985	Amplitude	0.988
	Latency	0.827	Latency	0.753

7.4: Discussion

7.4.1: Inter- and intra-session reliability. Atkinson and Nevill (1998) have characterised the quality of reliability measures, defining that ICC measures above 0.9 indicate “high” reliability, while those between 0.7 and 0.8 indicate “good” reliability and those between 0.6 and 0.5 indicate “moderate” reliability. While other researchers have suggested a wide range of definitions, the definitions proposed by Atkinson and Nevill were accepted as the standard for the presented comparisons.

Intra-session reliability measures of MEP amplitude and onset latency recorded within a single session are high for both conditions, when blocks of five trials are used to establish ICCs. Correlation coefficients decreased as the number of trials per block decreased, but even the lowest ICC value can still be considered “good”. These data are in agreement with prior research on MEPs derived from the abductor digiti minimi muscle (Christie et al., 2007), and indicate that five trials should optimally be included in analyses investigating MEP amplitude or onset latency.

For MEP amplitude, inter-session reliability coefficients established between Session 1 and each of the subsequent sessions ranged from moderate for five trials per block to high for 10 trials per block in both contraction conditions. Interestingly, reliability measures reached optimal values when 10 trials were included in the analysis, with a slight drop when all 15 trials were considered. As highest reliability was achieved for blocks of 10 trials, it appears necessary to include at least 10 trials into data analysis when the research paradigm includes multiple, independent sessions for data collection. Reliability measures recorded for MEP onset latencies indicate that averages of 15 trials produced highest reliability, although reliability measures for averages of 10 trials were still sufficiently high.

Reliability measures were slightly lower for inter-session comparisons of MEP amplitude compared to intra-session comparisons. This difference was not seen for reliability coefficients of MEP onset latency. It is possible that a small degree of variability in coil placement was introduced because of the necessity to identify the optimal scalp location for MEP elicitation during several independent data collection sessions, which would consequently influence MEP amplitude measures.

Studies including multiple sessions for data collection on the same research participant, which are not conducted on the same day, consequently requiring multiple identifications of the optimal TMS stimulation site, thus need to take particular care in identifying this site.

7.4.2: Inter- and intra-rater reliability. Both inter- and intra-rater reliability coefficients were consistently high for MEP amplitude measures. This is not unexpected as the identification of peak measures is inherently unambiguous. Similarly, high inter-rater reliability has been reported previously for pharyngeal manometry data, the analysis of which requires a similar process of identifying peak data points within a waveform (Doeltgen, Witte, Gumbley & Huckabee, 2009). Additionally, identification of peak data points in this research programme was facilitated by the data analysis software, as it required defining an area of interest around the peak data points, which were visually identified by the raters.

Values of inter-rater reliability for MEP onset latency were lower compared to the intra-rater reliability for this measure. The discrepancy in determining MEP onset may be due to electromyographic activity present in the waveform during muscle activation. While the documented ICC values are lower than those found for

identification of MEP amplitude, these values are still within a range that can be considered “good” (Atkinson & Nevill, 1998).

7.5: Conclusions

The inter- and intra-session reliability of task-related MEPs recorded from the submental muscle group using the novel data acquisition system and methods described in Chapter 6 is similar to that reported previously (McMillan et al., 1998a; Kamen, 2004; Christie et al., 2007). Further, the present analyses have documented that MEP amplitude and onset latency measures can be reliably identified within and between raters. Based on the data presented in this chapter, MEPs triggered by volitional swallowing and volitional contraction can be recorded reliably at the submental muscle group across multiple sessions, when the level of background activation is controlled for by means of threshold triggering from sEMG activity.

Chapter 8: The Effects of Repeated Volitional Swallowing and Time on MEP Amplitude and Onset Latency¹⁰

It has been shown that MEP amplitude increases in response to practicing a novel motor task. For example, MEPs recorded from the extensor pollicis brevis muscle increased after a repeated thumb extension exercise (Buetefisch et al., 2000). Similarly, Liepert, Graf, Uhde, Leidner and Weiller (2001) reported increased cortical motor map representation of the abductor pollicis brevis muscle after 1 hr of functional physical therapy. Fraser et al. (2003) documented that repeated water swallowing increases the excitability of cortical projections to the pharyngeal musculature. This change occurred immediately after task performance, but was not sustained at 30 min thereafter. In contrast, pharyngeal electrical stimulation was found to increase corticobulbar excitability for up to 60 min post stimulation, suggesting potential benefit for swallowing rehabilitation.

Interestingly, MEP amplitude increases associated with skill acquisition dissipate after the skill has been acquired or over-learned (Pascual-Leone et al., 1994; Muellbacher et al., 2002b). In this context, Thompson and Stein (2004) documented for the lower limb tibialis anterior and soleus muscles of 10 healthy research participants that 30 min of walking did not affect motor cortical excitability. It may be argued that walking is not a novel task, especially not for neurologically unimpaired individuals, and thus represents a heavily automated motor response. After 30 min of walking paired with electrical stimulation, which provided a novel task context through altered peripheral sensory feedback, a

¹⁰ The data presented in this chapter were collected in the context of two summer studentships held by Mr Ali Abu-Hijleh and Mr Aamir Al-Toubi, under the supervision of Mr Sebastian Doeltgen and Dr Maggie-Lee Huckabee. Data analysis and manuscript preparation for this chapter of this thesis were performed independently from any work related to the summer studentship.

significant increase in cortical excitability was observed. Together, these data indicate that the repeated performance of a novel task may induce changes in motor cortical excitability; however, the extent of those changes and their time course are dependent on the nature of the task.

Cortical excitability also varies across time within individuals, which may exaggerate, or mask, the effects induced by treatment. Intra-individual variability in cortical excitability has been shown to follow a cyclic pattern, with substantial fluctuations in MEP amplitude observed over a period of seconds or minutes (Wassermann, 2008, see also Figure 12, p. 108). Evaluation of MEP measures across the timeframe employed in this research programme (before and up to 90 min post treatment) may therefore be subject to intrinsic changes of cortical excitability, which are unrelated to treatment effects. In contrast, the reliability of mean MEP measurements has been documented to be high, indicating that averaging of multiple trials recorded over several seconds or even minutes minimises the effects of intrinsic variability (Plowman-Prine et al., 2008).

Investigation of the effects of repeated swallowing on the excitability of corticobulbar projections provides important baseline data for the methodologies employed in this research programme. It is possible that repeated volitional swallowing classifies as a “novel skill”, because the context and frequency of the repeated volitional swallowing condition, would not normally occur in every day situations. Additionally, exploration of the variability of MEP amplitude over time is warranted to ensure that identified changes post treatment are clearly treatment related and not due to intrinsic fluctuation of the measurement.

The aim of this study was therefore to identify the effects of repeated swallowing and time on corticobulbar excitability. Based on previous research findings, the following hypotheses were tested:

Hypothesis 2 (research protocol A): Repeated volitional swallowing, performed 60 times at a rate of one swallow per approximately 12 sec, will not increase corticobulbar excitability, as measured by increased MEP amplitude.

Hypothesis 3 (research protocol B): Mean MEP amplitudes averaged across 15 trials will not vary significantly across a 2 hr period.

8.1: Methods

8.1.1: Participants. A total of 15 young healthy participants were initially screened for MEPs [8 females, mean age 23.4 yrs (SD 4.8 yrs)]. The first 10 healthy participants who displayed discernable MEPs were recruited into this study (5 females, mean age 24.5 years (SD 5.9 yrs)]. All participants attended two sessions for data recording. Participants provided written informed consent and expressed full comprehension of the research procedures. Participants reported no medical history, current symptoms of dysphagia or neurological impairment and no drug use that would potentially affect their swallowing or neurological function.

8.1.2: Data recording and experimental protocols. Participants were connected to the data acquisition system as described in Chapter 6. Two submental electrodes and the reference electrode placed over the mandibular prominence at the base of the vertical ramus were mounted for this study. After the trigger threshold had been determined and the optimal scalp location for eliciting MEPs had been identified, 15 MEPs were recorded as baseline measures during each of two muscle contraction conditions: VC and VPS.

For research protocol A, participants were cued by a small light to complete 60 volitional saliva swallows, one performed every 12 sec. The intervention for this

experiment was swallowing. After completion of the intervention (approximately 25 min post baseline), MEPs were recorded at intervals of 5 min, 30 min, 60 min and 90 min, thereby evaluating changes in corticobulbar excitability in response to repeated swallowing.

For research protocol B, 15 MEPs were recorded during both VC and VPS every 30 min for 2 hrs, allowing for evaluation of changes in corticobulbar excitability across time. Data recorded at 5 min, 30 min, 60 min and 90 min post treatment were compared to data recorded at baseline (0 min). It is noteworthy that in protocol B, the “intervention” was a 25 min period of rest.

8.1.3: Data analysis. No significant trial effects were identified for any of the blocks of 15 trials (Appendices 6 & 7), except for the amplitude data recorded during VC at 30 min post treatment in protocol B. As no general pattern of trial effects was identified, mean amplitude and onset latency data of each set of 15 MEPs recorded during each muscle contraction condition (VC and VPS) at each assessment time (baseline and at 5 min, 30 min, 60 min and 90 min post treatment) were calculated. To control for inter-individual variability, MEP amplitude and onset latency measures were expressed as percentage of change from baseline. These relative measures were then subjected to repeated measures ANOVA.

8.2: Results

8.2.1: Amplitude. For protocol A, one-way repeated measures ANOVAs revealed no significant main effect of intervention (repeated swallowing) on MEP amplitude measures recorded during VC or VPS conditions [VC: $F_{(4, 36)} = 0.4$, $p = 0.81$; VPS: $F_{(4, 36)} = 0.54$, $p = 0.71$]. Likewise, no significant main effect of intervention (time) was identified for protocol B [VC: $F_{(4, 36)} = 1.23$, $p = 0.32$; VPS:

$F_{(4,36)} = 0.26, p = 0.90$]. Table 8 shows the mean and SD of MEP amplitudes recorded at baseline and at four post treatment assessments during the VC and VPS contraction conditions.

Table 8.

Mean and SD of MEP amplitude (in μV) across assessment times and protocols

Assessment time	Protocol A		Protocol B	
	VC	VPS	VC	VPS
Pre-treatment baseline	764.5 (326.4)	641.87 (472.88)	757.83 (307.6)	583.4 (193.6)
5 min post treatment trial	692.95 (331.07)	603.43 (309.38)	847.4 (339.54)	600.9 (252.8)
30 min post treatment trial	767.2 (438.4)	586.9 (359.17)	746.63 (327.53)	566.7 (231.94)
60 min post treatment trial	827.05 (510.7)	635.32 (354.5)	704.87 (363.6)	618.8 (266.75)
90 min post treatment trial	721.75 (430.4)	596.5 (354.46)	737.1 (308.85)	577.87 (208.42)

8.2.2: Onset latency. One-way repeated measures ANOVAs revealed no significant effects of either intervention on MEP onset latencies recorded during VC or VPS conditions [Protocol A: VC: $F_{(4,36)} = 0.61, p = 0.66$; VPS: $F_{(4,36)} = 1.56, p = 0.24$; Protocol B: VC: $F_{(4,36)} = 2.39, p = 0.07$; VPS: $F_{(4,36)} = 0.51, p = 0.73$]. Table 9 displays the mean and SD of MEP onset latencies recorded at baseline and at four post-treatment assessments during the VC and VPS contraction conditions.

Table 9. *Mean and SD of MEP onset latencies (in ms) across assessment times and protocols.*

Assessment time	Protocol A		Protocol B	
	VC	VPS	VC	VPS
Pre-treatment baseline	7.8 (0.42)	8.2 (0.94)	8.3 (0.96)	8.5 (0.93)
5 min post treatment trial	7.9 (0.6)	8.4 (0.84)	7.9 (0.71)	8.5 (1.08)
30 min post treatment trial	8.0 (0.75)	8.6 (0.74)	8.14 (0.66)	8.7 (0.73)
60 min post treatment trial	7.9 (0.77)	8.5 (0.82)	7.9 (0.89)	8.6 (0.84)
90 min post treatment trial	8.0 (0.53)	8.6 (0.78)	7.9 (0.83)	8.5 (0.84)

8.3: Discussion

This study evaluated changes in the excitability of corticobulbar projections to the submental musculature in response to repeated swallowing and across time. No significant effects of either variable were identified for MEP amplitude and onset latency measures recorded during both VC and VPS contraction conditions.

Prior research has indicated that MEP measures, in particular MEP amplitude, change in response to practicing a novel motor skill (Bueteffisch & Cohen, 2008). It was therefore a potential methodological confound that repeated volitional swallowing, a task that does not normally occur in every day situations, could affect MEP amplitude in a similar way. The data documented here indicate that this is not the case. Three explanatory hypotheses are offered in regard to this finding. One, it may be that swallowing does not constitute a “novel skill” (as it

naturally occurs many times throughout the day and night, for example, to clear ambient saliva and during meal times) and therefore does not increase corticobulbar excitability. This is in agreement with previous research, which documented no significant effect of walking, a highly automated and routine motor task, on corticospinal excitability (Thompson & Stein, 2004). Interestingly, 30 min of walking paired with electrical stimulation did affect corticospinal excitability, indicating that altered peripheral sensory feedback enhances motor cortical excitability even during (and up to 30 min after) an automated motor task. Whether electrical stimulation paired with repeated volitional swallowing has similar excitatory effects will be the objective of the investigations described in Parts V and VI of this thesis.

Two, participants in the study undertaken by Fraser et al. (2003), which documented an immediate increase in corticobulbar excitability after repeated water swallowing, performed 200 volitional water swallows, whereas in this investigation, only 60 repeated swallows were performed. It is therefore possible that motor cortical excitability was unaffected due to insufficient task repetitions.

Three, it may be argued that the repeated volitional swallowing paradigm in this study differed from occasional automatic saliva swallowing or even volitional deglutitive swallowing, in its high frequency and the volitional nature of its initiation. One could therefore expect that cortical networks such as the primary motor area would be affected by repeated performance of this task. The absence of changes in motor cortical excitability may therefore alternatively indicate that neural networks other than the primary motor area play a role in the initiation and execution of volitional swallowing. This hypothesis is supported by the data presented in Chapter 9 of this thesis and continues to warrant further investigation.

No systematic changes in mean MEP amplitudes were observed across a 2 hr period, which supports the documentation of high reliability observed in MEPs recorded from suprahyoid and pharyngeal muscles (Plowman-Prine et al., 2008) or submental muscles (Chapter 7) across several recording sessions, and corticospinal muscles, recorded across 1.5 hrs within the same recording session (Cacchio, Cimini, Alosi, Santilli, & Marrelli, 2009). However, trial-by-trial variability was observed and is reflected in the large standard deviations for MEP amplitudes. This variability has previously been attributed to fluctuations in the underlying excitability of cortical motor neurons (Wassermann, 2008). It may be argued that experimental circumstances such as inconsistent coil placement, varying TMS intensity or different levels of muscle pre-activation affected MEP amplitudes across the different trials. However, this is unlikely as experimental procedures were standardised (TMS intensity and TMS trigger threshold remained constant across all trials) and great care was taken to assure consistent coil placement across all assessments. In regard to the stability of mean MEP amplitude measures, it is likely that averaging reduced the degree of intra-individual short-term variability and therefore provides a suitable means for generating reliable measures of corticobulbar excitability across a 2 hr timeframe.

Similarly, no changes in MEP onset latencies across time were identified in this study, supporting the findings of high intra-session reliability reported in Chapter 7. This finding is also in agreement with previous reports of high reliability of MEP onset latencies recorded from limb muscles (Cacchio et al., 2009). Importantly, stable MEP onset latencies indicate a high reliability and consistency in coil placement, as previous research has shown that MEP onset latency changes as a function of coil placement (Carroll, Riek & Carson, 2001). This consequently lends further support to the hypothesis that the variability in MEP amplitudes is most

likely related to fluctuations in intrinsic motor cortical excitability, and not variability in coil placement.

Taken together, the findings documented in this study provide valuable baseline information for subsequent investigations undertaken in the framework of this research programme. Averaged MEP amplitude and onset latency are not affected by repeated swallowing and do not vary significantly as a function of time. Potential changes in MEP amplitude or latency, observed in response to NMES intervention, will therefore most likely reflect treatment-induced modifications of the excitability of tested neural pathways. In addition, the absence of changes induced by repeated swallowing may indicate that neural networks other than direct pyramidal pathways are involved in the initiation and execution of this task.

PART IV

Chapter 9: Task-Dependent Differences in the Excitability of Corticobulbar Projections to the Submental Musculature: Implications for Neural Control of Swallowing¹¹

Motor evoked potentials recorded from muscles involved in swallowing have been investigated as a measure of excitability of the corticobulbar pathways. Fraser et al. (2002) and Power et al. (2004) have recorded MEPs from the musculature underlying the pharynx and faucial pillars, respectively, to infer treatment effects after application of electrical stimulation to these muscles in healthy volunteers and individuals with dysphagia. Effects were found to be dependent on the frequency of stimulation, with some frequencies facilitating and others inhibiting MEP amplitude for up to 60 min post treatment. Optimal stimulation frequencies were different for the two muscle groups. Importantly, both studies documented that a change in the excitability of the corticobulbar projections to the muscles of interest was directly related to improved (Fraser et al., 2002) or deteriorated (Power et al., 2004) swallowing function. Fraser et al. (2002) showed that, in individuals with dysphagia, an increase in pharyngeal corticobulbar excitability after 5 Hz non-event-related NMES was directly related to a reduction in pharyngeal transit time, swallowing response time and aspiration score. In contrast, Power et al. (2004) found that corticobulbar inhibition after 5 Hz non-event-related NMES of the faucial pillars

¹¹ A modified version of this chapter is pending submission for publication in *Clinical Neurophysiology*.

correlated with radiographically documented evidence of swallowing impairment (significantly increased swallowing response time) in normal research participants.

In a clinical study of two groups of stroke patients with either aspiration or pharyngeal residue, Gallas et al. (2007) studied MEPs recorded from mylohyoid muscles to investigate the effects of chronic stroke on MEP amplitude and onset latency. Subjects with aspiration displayed longer ipsilateral MEP onset latencies and lower MEP amplitudes than subjects without dysphagia in the control group or subjects with pharyngeal residue. Contralateral MEPs had lower amplitudes in both patient groups compared to the healthy control group. In agreement with previous research on the pharyngeal musculature (Hamdy et al., 1996), this study further documented differences in the excitability of corticobulbar projections from the two hemispheres, with TMS over one hemisphere evoking larger MEP amplitudes than over the other hemisphere. In summary, these data document an important relationship between MEPs of corticobulbar muscles and swallowing function.

In the abovementioned studies, MEPs were recorded when the muscles of interest were *at rest*. No previous studies have investigated MEPs recorded from the submental muscle group (anterior belly of digastric, mylohyoid and geniohyoid) during pre-activation. However, literature suggests that this approach would be of benefit for several reasons. Firstly, evaluating MEPs during functional tasks may provide greater insight into task-related differences in corticobulbar excitability, ultimately reflecting the degree of cortical contribution to the motor control of these tasks.

Secondly, background activation is known to have a facilitatory effect on the amplitude of MEPs recorded not only in limb muscles (Rothwell et al., 1991; Maertens de Noordhout et al., 1992) but also in facial muscles (masseter muscle)

(McMillan et al., 2001). Additionally, researchers have reported that muscle pre-activation is essential for eliciting MEPs in a number of facial muscles (Macaluso et al., 1990; McMillan et al., 2001), including the mylohyoid muscle (Cruccu et al., 1989), which is part of the submental muscle group involved in swallowing. Pre-activation may therefore allow measurement of larger corticobulbar MEPs in a greater number of subjects.

Thirdly, the degree of corticobulbar excitability may be task-dependent, allowing insight into differences in the neural control of these tasks. The orchestrated execution of muscle contraction during the pharyngeal phase of swallowing is coordinated by central pattern generators in the brainstem (Jean, 2001). The primary motor area has been unambiguously linked to volitional oral movements such as required for bolus preparation (Kern, 2001b). Additionally, a contribution of the primary motor cortex to the pharyngeal phase of volitional swallowing has been implicated by fMRI (Martin et al., 2001; Martin et al., 2004; Hamdy, 1999a; Suzuki, Asada, Ito, Hayashi, Inonue & Kitano, 2003; Toogood et al., 2005; Kern et al., 2001a; Kern et al., 2001b). This research is contrasted by studies employing EEG, which documented a relative quiescence of M1 during volitionally initiated pharyngeal swallowing, based on an absence of the second component of the Bereitschaftspotential (BP, or readiness potential) that is known to correlate with transfer of the motor plan to M1 (Huckabee et al., 2003). In a similar study of BP, Satow et al. (2003) reported lower post-movement potentials for volitional swallowing compared to a tongue protrusion task, suggesting that M1 may not contribute as substantially to movement processing for volitional swallowing.

The extent and functional involvement of the primary motor cortex in swallowing neural control have not yet been clearly defined. Comparison of cortical excitability related to volitional and reflexive components of swallowing has been

suggested as a valid approach to investigating the nature of cortical contributions to swallowing motor control. Kern et al. (2001a) state “since there is no volitional input for initiation of a reflexive swallow, comparison of its cortical representation with that of volitional swallow can provide a study model that can potentially increase our understanding of the non-sensory/motor cortical control of swallowing” (Kern et al., 2001a, p.354). In the context of this research programme, differing levels of corticobulbar excitability would be reflected in differences in MEP amplitude. In contrast, if M1 is activated during both the volitional contraction and swallowing tasks in similar ways, MEP amplitude would be expected to be comparable between the different tasks.

The above considerations led to the following hypothesis:

Hypothesis 4: Submental MEPs recorded during muscle pre-activation will differ in amplitude between the three motor tasks (VC, VPS and RPS). Motor evoked potential amplitude will be larger during VC compared to MEP amplitudes recorded during the two swallowing conditions. Onset latencies of submental MEPs will not differ between conditions.

9.1: Methods

9.1.1: Participants. Thirty-five young, healthy subjects were recruited into the study [24 females, 30.1 yrs, (SD 8.4yrs)]. Subjects provided written informed consent and reported full understanding of the research procedures they were asked to perform. Subjects were neurologically unimpaired and reported no contraindications to TMS on the Transcranial Magnetic Stimulation Safety Screen (Keel et al., 2000). This study was approved by the appropriate institutional health ethics review board.

9.1.2: Data acquisition. After the skin surface was cleaned with an alcohol swab, two surface electrodes (BRS-50K, Blue Sensor™, Ambu, Denmark) were placed at midline over the submental muscle group. Electrode placement procedure was standardised by placing the anterior electrode first with its anterior edge directly behind the bony aspect of the mandible and with 1 cm overlapping lateral to midline. The second electrode was mounted behind the anterior electrode with a gap of 5 mm between electrodes. sEMG activity was therefore recorded from both left and right midline portions of the mylohyoid, left and right anterior belly of digastric and left and right geniohyoid muscles. Submental muscle group MEPs were investigated because this muscle group is critically involved in facilitating anterior displacement of the hyoid during swallowing which subsequently facilitates epiglottic deflection for airway protection and opens the upper oesophageal sphincter. Additionally, the submental muscle group is the target of a number of treatment approaches in dysphagia management [e.g., head lift manoeuvre (Shaker et al., 1997), effortful swallow (Logemann, 1983) or electrical stimulation (Freed et al., 2001)] highlighting its importance in the execution of effective swallowing. A ground electrode was attached to the bony mandibular prominence at the base of the vertical ramus. All three electrodes were connected to an amplifier (Dual Bio Amp, ML 135™, ADInstruments, Castle Hill, Australia) and recording system (Powerlab 8/30™, ML 870, ADInstruments). The sampling rate for data acquisition was 10 kHz and data were high pass filtered at 10 Hz. sEMG activity was recorded for a period of 200 ms when the magnetic stimulator (Magstim 200™, Magstim Company Limited, Whitland, Wales) was discharged, recording 50 ms pre- and 150 ms post-trigger.

9.1.3: Transcranial magnetic stimulation of submental motor cortex. Focal cortical stimulation was achieved using a figure-of-8 coil with an outer wing diameter of 70 mm and a maximal output of 2.2 Tesla. A custom-built trigger system was designed to discharge the magnetic stimulator. Surface EMG activity in the submental muscles was monitored by the triggering system, which discharged the magnetic stimulator when a pre-set trigger threshold was breached. The trigger threshold was determined for each individual prior to data collection by calculating 75% of the mean maximal sEMG amplitude recorded during 10 volitional saliva swallows that were executed with minimal or no volitional orolingual movements. Setting the threshold to this value assured that the stimulator was discharged at the onset of a volitionally initiated pharyngeal swallow rather than during oral preparatory movements. The same trigger threshold was maintained in the volitional contraction and reflexive swallowing conditions to assure that the underlying degree of muscle pre-activation was the same in all conditions. The trigger device was automatically disabled for 10 s after each stimulus to prevent elicitation of a trigger impulse not associated with target motor behaviour.

Prior to data collection, the optimal scalp site for consistently eliciting the largest submental MEP, measured from the first positive to the first negative peak, was identified for both hemispheres. An area approximately 4 cm anterior and 8-10 cm lateral to the cranial vertex was searched systematically for this location. Magnetic stimulator intensity was set to 60% maximal stimulator output and subjects contracted their muscles volitionally in order to discharge the stimulator (via trigger device). If no MEPs could be detected, stimulator output was increased in 10% increments until discernable MEP responses could be recorded. Subsequent to identification of the optimal scalp location, maximal MEP amplitude was identified for this site on each hemisphere by increasing TMS intensity until no

increase in MEP amplitude was observed or 100% stimulator output was reached. Data were collected from the hemisphere over which largest MEPs could be evoked. Stimulator output for subsequent data collection was set to the value at which MEPs of 50% of maximal amplitude were elicited. For each condition, 15 MEPs were recorded and averaged for analysis.

9.1.4: Muscle contraction conditions. In all subjects, data were recorded in counterbalanced order for two conditions of muscle pre-activation: volitional contraction and volitional swallowing. In a subset of 19 subjects, MEPs were additionally recorded during reflexive swallowing. In this subset, MEP recordings were randomised across conditions. For the volitional contraction task, subjects were instructed to “contract the muscles under your chin as if stifling a yawn”. For volitional swallowing, subjects were asked to “swallow your saliva as you normally would”. During performance of these two volitional conditions, subjects were instructed to keep their tongue as quiet and relaxed as possible. Visual feedback about the degree of muscle contraction was given to subjects by means of online sEMG. Subjects were asked to observe their submental muscle activity displayed on-screen and to match the degree of muscle activity during volitional contraction to the degree of muscle contraction displayed during swallowing. Subjects practiced the contraction tasks, alternating between swallows and contractions, for approximately 5 min prior to data collection.

For the reflexive swallowing condition, a small, flexible tube¹² (2 mm diameter) was placed into the posterior aspect of the participant’s oral cavity, with the opening of the tube resting approximately at the level of the base of the tongue.

¹² A winged infusion set (‘butterfly needle set’) was attached to a 10 ml syringe and the needle was cut off at the end of the flexible tube.

Subjects were asked to close their eyes to deter visual cuing and 1 ml of room temperature water was infused onto the base of tongue at random intervals, eliciting a reflexive swallow. Trials that did not elicit a swallow or induced coughing or throat clearing were deleted and repeated.

9.2: Results

In 13 subjects (38%), no MEPs could be elicited for any condition. In the remaining 22 subjects (62.8%), discernable MEPs could be recorded during the volitional contraction condition; MEPs were recorded during the volitional swallowing condition in only 16 of these subjects (45.7%). Chi-square analysis revealed no significant difference between occurrences of MEPs across the two tasks in this participant cohort ($\chi^2 = 1.44, p = 0.23$).

Motor evoked potentials during reflexive swallowing were additionally investigated in 19 subjects but could only be recorded in six of these subjects (31.6%). In this sub-sample, MEPs could be recorded during volitional contraction in 15 subjects (78.9%) and in eight subjects (42.1%) during the volitional swallowing task. Chi-square analysis revealed a significant difference of MEP occurrences across the three tasks ($\chi^2 = 9.4, p = 0.009$). Comparing two tasks independently, MEPs were more likely to be recorded during volitional contraction than during either volitional swallowing ($\chi^2 = 3.96, p = 0.046$) or reflexive swallowing ($\chi^2 = 6.812, p = 0.009$). Between the two swallowing conditions, occurrence of MEPs was not significantly different ($\chi^2 = 0.74, p = 0.113$).

9.2.1: MEPs recorded during VC versus MEPs recorded during VPS. Due to the small sample size for which MEP data were available for all three conditions, statistical comparisons of MEP amplitude and onset latency measures were only

performed on the data of the 16 subjects that displayed MEPs during the volitional contraction and volitional swallowing tasks. Repeated measures analysis of variance (ANOVA) identified no trial effects for amplitude or onset latencies in any condition [volitional contraction MEP amplitude ($F_{(14, 210)} = 0.78, p = 0.68$), volitional contraction MEP onset latency ($F_{(14, 210)} = 0.70, p = 0.77$); volitional swallowing MEP amplitude ($F_{(14, 210)} = 1.1, p = 0.4$), volitional swallowing MEP latency ($F_{(14, 210)} = 1.4, p = 0.16$)]. Therefore, averaged data for each participant were used in subsequent analyses.

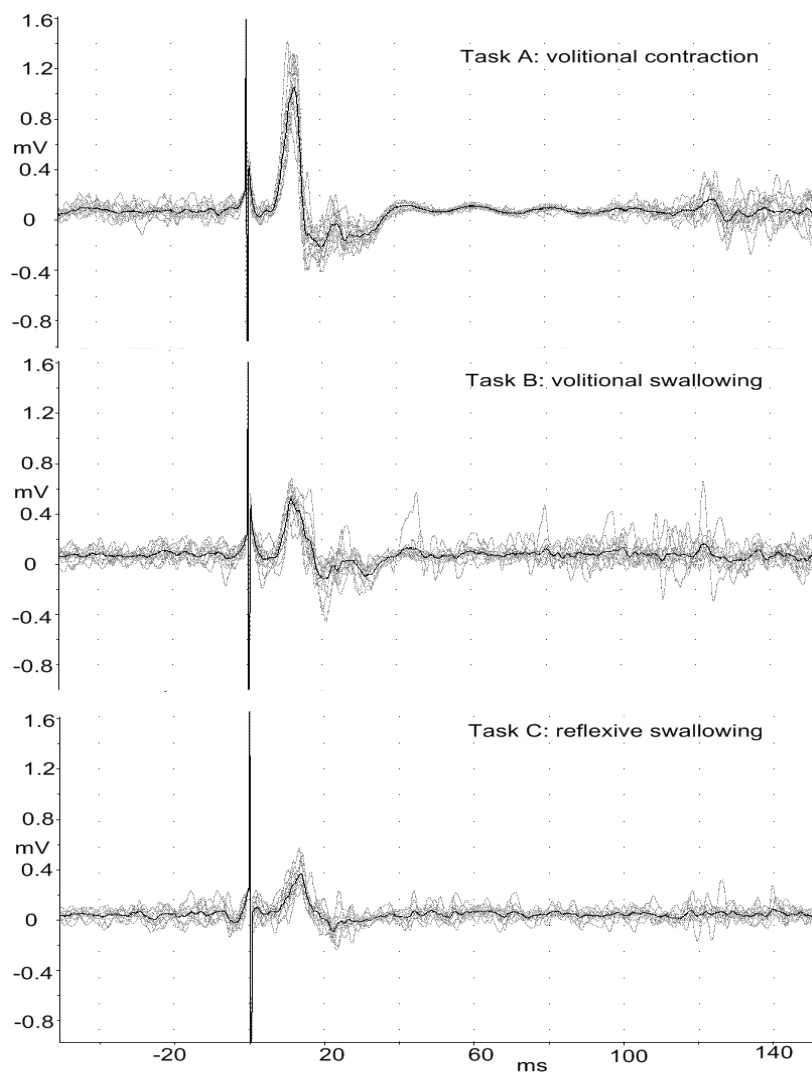
Resting sEMG levels were calculated for a period of 80 ms prior to onset of task-related muscle activity and did not differ across conditions [volitional contraction: 0.035 mV (SD: 0.031 mV); volitional swallowing: 0.036 mV (SD: 0.027 mV); $t_{(239)} < 1.0, p > 0.05$]. Trigger thresholds used for eliciting TMS during both conditions were identical within each subject. Mean trigger threshold across subjects was 0.16 mV (SD 0.05 mV).

9.2.2: MEP amplitude. A two-tailed paired-samples t-test revealed a significant difference in peak to peak amplitudes between conditions ($t_{(15)} = 3.1, p = 0.008$), with greater mean amplitude for MEPs elicited by volitional contraction [841.8 μ V (SD 365.4 μ V)] than those elicited by volitional swallowing [607.4 μ V (SD 207.7 μ V)]. The effect size of this comparison is considered “large” (Cohen, 1988) at $d = 0.789$. Figure 21 depicts averaged MEP waveforms of all conditions recorded from one representative participant.

9.2.3: MEP onset latency. A two-tailed paired-samples t-test revealed no significant difference in onset latencies between conditions [$t_{(15)} = 1.4, p = 0.18$],

voluntary contraction MEP mean onset latency: 8.6 ms (SD 1.2 ms); swallowing MEP mean onset latency: 9.1 ms (SD 1.6 ms)].

Figure 21. Motor evoked potential waveforms of one representative research participant. The 15 superimposed waveforms and the average waveform (in bold) are displayed. MEPs were triggered from submental sEMG during a volitional contraction task (A), and muscle contraction at the onset of the pharyngeal phase of a volitional swallow (B) or a reflexive swallow (C). The vertical line at 0 ms displays the magnetic stimulus artefact. Note a rise in sEMG activity from resting baseline just prior to TMS elicitation.



9.3: Discussion

In this study, corticobulbar excitability during execution of three conditions of muscle pre-activation was evaluated in order to elucidate the degree of primary motor cortex involvement in the pharyngeal phase of swallowing. In 13 subjects, no discernable MEPs could be recorded. A similar phenomenon has been reported previously for the biceps brachii muscle in response to TMS of the corresponding area of the contralateral M1 (Ziemann et al., 1998). In the remaining subjects, MEPs were detected most consistently during the voluntary muscle contraction task, a task that would recruit corticobulbar pyramidal pathways from M1 to the periphery. They were less frequently detected and were smaller in amplitude for the volitional swallowing condition. Furthermore, MEPs were infrequently detected during pre-activation by reflexive swallowing, a task that is governed by brainstem central pattern generators (Jean, 2001). Given that the amplitude of MEPs recorded during muscle pre-activation reflects the state of excitability of the pyramidal pathway (Rothwell et al., 1991), these data provide valuable new insights into the contribution of corticobulbar excitability for swallowing.

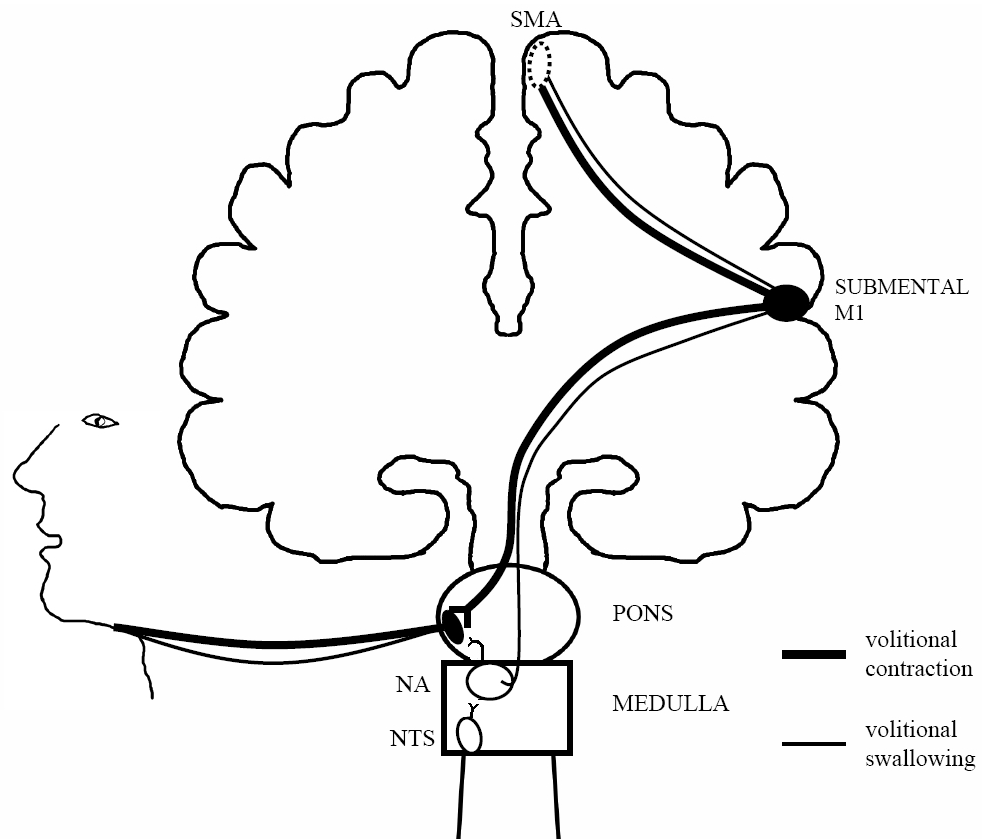
Two hypotheses are proposed in explanation of the observed differences in MEP facilitation. These are discussed in the context of two proposed models of swallowing motor control, specifically (1) the “Pyramidal Cortical Control” and (2) the “Non-Pyramidal Cortical Modulation” models of swallowing neural control. The pyramidal cortical control model proposes that M1 is actively involved in the execution of the pharyngeal phase of swallowing. Cortical motor output for swallowing descends along the same neural pathway as during a purely voluntary task, for example volitional contraction, and that differences in MEP amplitude are secondary to varying degrees of cortical motor output between these tasks (Figure 22). The non-pyramidal cortical modulation model argues that volitional contraction

and volitional swallowing are governed by distinctly different neural networks and that M1 is not, or is only marginally, activated during the pharyngeal phase of swallowing (Figure 23).

The pyramidal cortical control model describes the motor control of volitional contraction and volitional swallowing as being governed in essentially similar ways. The supplemental motor area (SMA) activates motor neurons of M1 associated with the submental musculature, which subsequently generates a descending volley that activates the muscles in the periphery (Cunnington, 1996). In this model, the same suprabulbar pathways are activated for volitional contraction and volitional swallowing. The differences in corticobulbar facilitation (and consequently MEP amplitude) are related to differences in the strength of the descending suprabulbar volley. As the contraction task is purely voluntary, greater neural output to motor neuron pools in the brainstem results in greater pre-activation of the neural pathway and ultimately greater facilitation of MEP amplitude. The reduced facilitation of MEP amplitude during volitional swallowing may be explained by the recruitment of a smaller number of suprabulbar motor neurons.

Figure 22.

Pyramidal Cortical Control Model. For both the volitional contraction (VC) and volitional swallowing conditions (VPS), neural activation is projected from the SMA to cranial nerve motor nuclei via the submental primary motor area (M1). Descending supra-bulbar volleys recruit a larger number of motor neurons during the volitional contraction condition compared to the volitional swallowing condition.



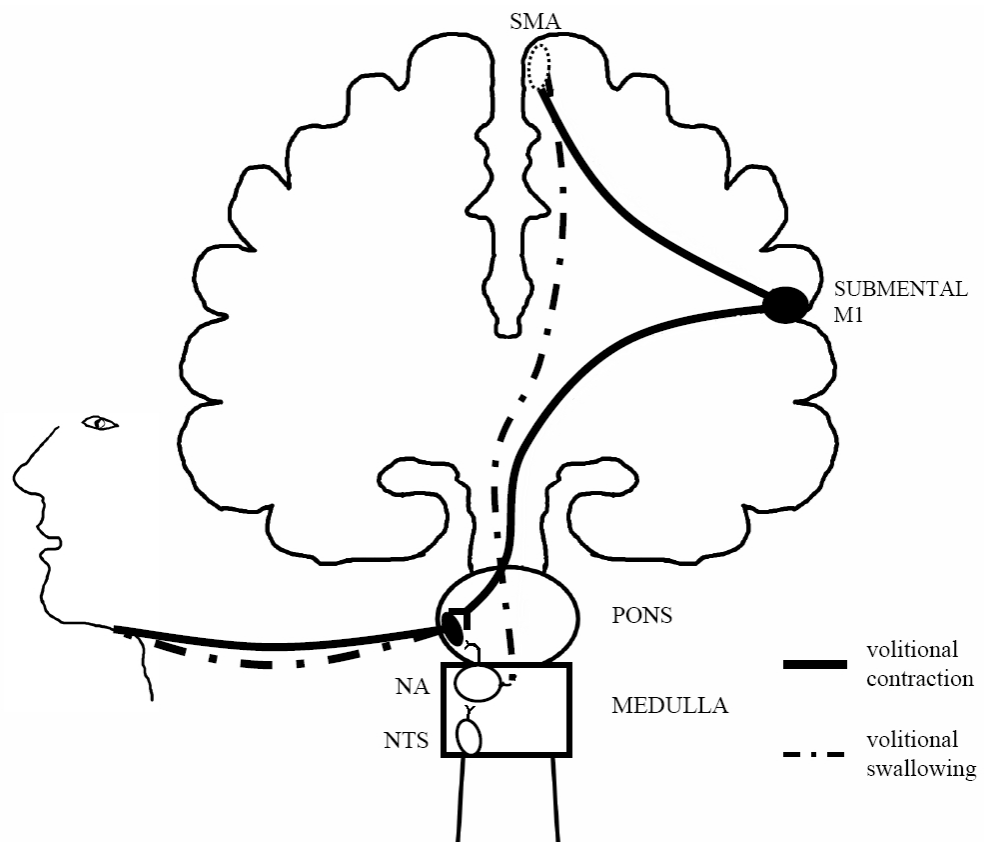
In support of the pyramidal cortical control model, a study employing fMRI has documented activation of M1 during volitional swallowing and volitional tongue elevation, however, the degree of cortical activation during volitional swallowing was lower than during the tongue elevation task (Martin et al., 2004). This finding is contrasted by reports of similar levels of cortical activation during volitional swallowing and non-deglutitive motor tasks such as jaw clenching, lip pursing and

tongue rolling (Kern et al., 2001b). However, large voxel size and the limited temporal resolution of fMRI may have obscured differentiation between tasks and failed to rule out the contribution of oral phase movements to M1 activation.

The non-pyramidal cortical modulation model describes the motor control of volitional contraction of submental muscles and reflexively initiated contraction of the same muscles during pharyngeal swallowing as governed by two distinctly different neural networks. The motor control of volitional contraction occurs as described in the pyramidal cortical control model. In contrast, pharyngeal swallowing is hypothesised to rely more heavily on the brainstem generated motor programme, with only marginal suprabulbar modulation of pharyngeal swallowing by M1. As swallowing-related MEPs were triggered at the onset of the pharyngeal phase of swallow, it is postulated that corticobulbar pathways were not pre-activated, or were only marginally pre-activated, immediately prior to and during MEP elicitation. According to this model, activation of the SMA directly excites the swallowing pattern generators located in the medulla of the brainstem. Contraction during the pharyngeal phase of volitional swallowing is thus heavily modulated by the SMA but is executed by the brainstem swallowing pattern generator. Lower amplitude of MEPs triggered by volitional swallowing relates to the relative inactivity of the submental M1, compared to that present for volitional contraction.

Figure 23.

Non-pyramidal Cortical Modulation Model. The volitional contraction (VC) and volitional swallowing conditions (VPS) are governed by two different supra-bulbar pathways. Volitional contraction neural activation is projected from the SMA to cranial nerve motor nuclei via the submental primary motor area (M1). For volitional swallowing, SMA directly activates motor neurons in the nucleus ambiguus while essentially bypassing the submental primary motor area (M1).



In support of the non-pyramidal cortical modulation model, studies investigating swallowing-related cortical pre-motor planning (Huckabee et al., 2003) and cortical post-movement potentials (Satow et al., 2003) have indicated a relative quiescence of the motor cortex during pharyngeal swallowing tasks. Further support for this model can be derived from the data recorded in the sub-sample that

performed all three contraction tasks. In these subjects, MEPs were more likely detectable during the volitional contraction task than during either of the swallowing tasks. As pre-activation of corticobulbar pathways facilitates MEP amplitude (Rothwell et al., 1991), the absence of MEPs during the swallowing conditions can be interpreted as evidence of a relative quiescence and thus, decreased excitability of the corticobulbar pathway. The finding that in the larger sample MEP amplitude was significantly smaller during the swallowing task than during the volitional contraction task further supports this hypothesis. It is worthy to note that a conservative approach was taken in this analysis by excluding the data of the six subjects that had measurable MEPs during the volitional contraction condition but not during the volitional swallowing condition. Had these subjects been included into the statistical analysis by assigning them a “0 μV ” score for absent volitional swallowing MEPs, as has been described previously (Gallas et al., 2007), then the effect size of this difference would have been substantially greater.

Likely, different stages of swallowing are governed by different neural networks. Thus, a single model to explain the complexity of swallowing is implausible. Activation of the primary motor area is required for volitional movements involved in bolus manipulation in the oral stage of swallowing (Kern et al., 2001b). The data presented in this subchapter indicate that the execution of the more reflexive, pharyngeal phase of swallowing is only marginally modulated by primary motor regions, consistent with the non-pyramidal cortical modulation model, and probably primarily governed by brainstem swallowing centers (Jean, 2001).

One might propose an alternative explanation of a methodological nature to explain the observed differences in MEP facilitation between the three tasks: that the level of muscle contraction at the time of MEP elicitation by TMS differed between

conditions. Indeed, it has been shown that maximal volitional contraction is greater than that recorded during volitional swallowing (Youmans & Stierwalt, 2006).

However, in the present study, subjects were carefully instructed to match the level of muscle contraction during the three conditions, identical TMS trigger thresholds were used for all conditions and resting muscle activity immediately pre-trigger was nearly identical. Muscle activation at the time of MEP elicitation was therefore comparable between these tasks, justifying the hypothesis that processes other than the level of peripheral muscle contraction affected MEP facilitation.

9.4: Conclusions

The presented data document differences in the degree of corticobulbar excitability during volitional contraction of the submental muscles and the contraction of this same muscle group during the pharyngeal phase of both volitional and reflexive swallowing. In support of the proposed non-pyramidal cortical modulation model, these differences indicate differing roles of M1 during execution of these tasks and provide valuable new insights into the contribution of corticobulbar excitability to swallowing motor control. Further research into the relative contribution of the motor cortex to the motor control of the heavily intertwined oral and pharyngeal phases of swallowing is warranted.

PART V

Chapter 10: Effects of Stimulus Frequency on the Excitability of Submental Corticobulbar Projections¹³

Research into the effects of NMES on cortical MEPs has documented that changes in this measure are frequency-specific with optimal stimulation parameters differing based on anatomical sites. In healthy research participants, Fraser et al. (2002) documented that the amplitude of MEPs recorded from the muscles underlying the pharyngeal mucosa increased in response to NMES administered at 5 Hz and decreased after 20 Hz and 40 Hz NMES compared to pre-treatment baseline. Power et al. (2004) reported similar frequency-specific findings after NMES of the muscles underlying the faucial pillars in healthy participants. However, in contrast to the results reported by Fraser et al. (2002), excitatory stimulation frequency was found to be 0.2 Hz, with 5 Hz NMES resulting in inhibition of MEPs. Importantly, this study documented that inhibitory NMES of the faucial pillar muscles resulted in increased swallowing response time in healthy research participants. Fraser et al. (2002) documented that individuals with dysphagia displayed a decrease in swallowing response time, pharyngeal transit time and aspiration score after NMES using optimal, excitatory stimulation parameters. The relationship of corticobulbar excitability and swallowing function documented in both studies underscores the importance of furthering our understanding of the precise effects of NMES on neurophysiological and functional measures of swallowing function.

¹³ The results reported in this chapter have been presented at the Annual Meeting of the Dysphagia Research Society, in Charleston, SC, 2008, where the author was awarded 2nd Place in the New Investigators Forum.

Based on these findings, it is possible that optimal stimulation parameters exist for other muscles involved in the act of swallowing, including the submental muscle group. To date, evaluation and identification of optimal NMES parameters for this muscle group have received no attention. It was therefore the primary goal of this research programme to investigate the effects of various NMES treatment protocols on MEPs recorded from these muscles. In subsequent chapters, the effects of a variety of NMES parameters, including stimulus frequency, stimulus train duration and number of repetitions (dose), and task context, are reported. This chapter presents the effect of “stimulus frequency” on MEP amplitude and onset latency.

This investigation differed from most previous research in two important ways. One, this study evaluated the effects of *event-related* NMES, which means that NMES was triggered by and provided during a volitional swallow. This is based on evidence from research in other areas of rehabilitation medicine, which suggests that NMES delivered during performance of a purposeful task may yield greater functional benefits than NMES provided to muscles at rest (Bax et al., 2005; Glanz et al., 1996; Bolton et al., 2004).

Two, MEP treatment outcome measures were elicited by two conditions of muscle pre-activation, specifically volitional contraction of floor of mouth muscles (VC) and contraction of the same muscles during the pharyngeal phase of volitional swallowing (VPS, volitional pharyngeal swallowing). The corticobulbar MEPs investigated by Fraser et al. (2002) and Power et al. (2004) were recorded when the muscles of interest were at rest. Measuring MEPs elicited in the context of motor tasks will allow interpretation of changes in corticobulbar excitability in a functional context. Further, it has previously been suggested that differences may exist in the

motor control of these two tasks (Chapter 9) and they may, therefore, respond differentially to NMES treatment.

The aim of this study was to identify the optimal event-related NMES stimulation frequency for the submental muscle group. NMES was administered at four frequencies and submental MEPs recorded during two muscle contraction conditions. The following hypothesis was tested:

Hypothesis 5 (research protocols 1 to 4): Changes in MEP amplitude in response to NMES treatment will be frequency-dependent, with some frequencies facilitating and others inhibiting MEP amplitude. Motor evoked potential onset latencies are not expected to change.

10.1: Methods

10.1.1: Participants. Fourteen young healthy adults [mean age: 27.1 yrs; (SD 2.7 yrs), 8 females, 10 right-handed (Oldfield, 1971)] were initially screened for MEPs. Four participants were excluded because of the inability to identify MEPs during both contraction conditions. Therefore, ten young, healthy adults were included [mean age: 27.5 yrs; (SD 2.9 yrs), 7 females, 7 right-handed (Oldfield, 1971)] and attended a total of four sessions each. Participants gave written informed consent and expressed full comprehension of the research procedures. Participants had no medical history or current symptoms of dysphagia, and reported no neurological impairment and no drug use that would potentially affect their swallowing or neurological function. This study received ethical approval from the appropriate Human Ethics Review Committee.

10.1.2: Pre treatment preparation and baseline recording. Participants were connected to the data acquisition system as described in detail in Chapter 6. Two submental surface electrodes, two surface electrodes over the thyrohyoid muscles and the reference electrode at the mandibular prominence at the base of the vertical ramus were mounted for this study. The individual's pain threshold for NMES was then established by delivering a continuous electrical current through the submental surface electrodes. Stimulation intensity commenced at a level of 1 mA and was increased in 3 mA increments until the participant reported a painful sensation and that a further increase in stimulus intensity could not be well tolerated. Each level of intensity was provided for at least 10 s to allow the participant to accommodate to the increased sensation. Intensity for subsequent NMES treatment was set to 75% of the individual's pain threshold.

An automated trigger system monitored *thyrohyoid* sEMG activity and elicited NMES treatment to the collective submental muscle group when a pre-set threshold was breached. Trigger threshold was determined for each participant as 75% of the mean thyrohyoid sEMG activity (in μV) of 10 noneffortful saliva swallows. This value was chosen as it represents thyrohyoid sEMG activity related to the pharyngeal phase of swallowing and rarely produced elicitation of a trigger impulse from sEMG activity during rest periods. The same trigger system also monitored *submental* sEMG activity and activated TMS (eliciting MEPs as outcome measures) when a pre-set threshold was breached. This threshold was set for each participant to 75% of the mean submental sEMG activity (in μV) of 10 noneffortful saliva swallows. Both thresholds were identified at the beginning of each of the four data acquisition sessions to compensate for slight differences in electrode placement.

After each production of a trigger impulse, the device automatically disabled subsequent impulses for 10 s in order to avoid eliciting triggers that were not related

to target motor behaviour. This 10 s rest period was indicated by a small light on the trigger device. Research participants observed this light and swallowed at their own pace after the light had switched off. Therefore, research participants swallowed at a rate of no less than approximately every 12 s. No participant reported difficulty swallowing at this rate.

Following this, the optimal scalp location for eliciting MEPs was identified as described in detail in Chapter 3. After conclusion of these preparatory procedures and before commencement of NMES treatment, 15 MEPs were recorded during both the VC and VPS contraction conditions as baseline measures.

10.1.3: Research protocols (1 to 4). After recording of baseline measures, event-related NMES was administered using the following stimulus parameters.

- stimulation frequency: 5 Hz, 20 Hz, 40 Hz or 80 Hz
- stimulus train duration: 4 s
- pulse (stimulus) characteristics: 200 μ s square pulse
- stimulation intensity: 75% of the individual's pain threshold
- repetitions: 60 stimuli trains (each triggered by a volitional saliva swallow)

Across the four sessions, the variable of frequency was randomly assigned and all other parameters held constant to evaluate optimal stimulation frequency.

10.1.4: Post treatment outcome measurement. Subsequent to the treatment period, 15 MEPs were recorded during each of the muscle contraction conditions. Post treatment, further counter-balanced sets of 15 MEPs for each condition were recorded at 30 min, 60 min and 90 min. Similar intervals of post treatment outcome measurement were investigated by Fraser et al. (2002) and Power et al. (2004) who

documented that an effect on MEP amplitude in response to NMES evolved over a 60 min post treatment period.

10.1.5: Data preparation and analysis. Statistical analyses were performed on the averaged data of each block of 15 MEP trials of each muscle contraction condition (VC and VPS) for each participant. Before calculating these means, a repeated measures ANOVA was undertaken on the blocks of individual trials to identify potential trial effects. As no significant trial effects were identified ($p > 0.05$ for all comparisons, Appendices 6 & 7), all blocks of 15 MEP trials were collapsed to mean values. To control for inter-individual variability, MEP amplitude and latency measures were expressed as a percentage of change from baseline. Two-way repeated measures ANOVAs were performed on these relative values with the independent variables of “Frequency” (5 Hz, 20 Hz, 40 Hz, and 80 Hz) and “Time post treatment” (5 min, 30 min, 60 min, and 90 min) as repeated measures. ANOVAs excluded baseline data (100% of pre treatment performance), as these had no variance. Analyses were undertaken separately for amplitude and latency measures recorded during each of the two muscle contraction conditions (volitional contraction and volitional swallowing).

10.2: Results

10.2.1: MEP amplitude. Two-way repeated measures ANOVA of the MEP amplitude data recorded during volitional contraction using the variables Frequency and Time revealed a significant interaction of Frequency and Time ($F_{(9,81)} = 2.6$, $p = 0.011$) (Figure 24). Post-hoc paired-samples t-tests comparing the amplitude measures of each post treatment recording with the respective pre-treatment baseline for each frequency revealed that, after 80 Hz stimulation, MEP amplitude was

significantly increased at 30 min post treatment ($t_{(9)} = 2.9$, $p = 0.017$) and 60 min post treatment ($t_{(9)} = 3.9$, $p = 0.003$). In contrast, MEP amplitude was significantly decreased at 60 min post treatment after 20 Hz stimulation ($t_{(9)} = 2.3$, $p = 0.048$) and 5 Hz stimulation ($t_{(9)} = 2.9$, $p = 0.017$). (Figure 24). The largest effect size was found for the effect of 80 Hz stimulation at 60 min post treatment which was $d = 1.77$. Significant quadratic trends were documented for post treatment effects after 5 Hz ($p = 0.029$) and especially 80 Hz NMES ($p = 0.006$), with temporarily increased MEP amplitudes observed after 80 Hz NMES and temporarily decreased amplitudes observed after 5 Hz NMES. The 40 Hz NMES appeared to have no clear effects.

During the volitional swallowing condition, no effects on MEP amplitude were observed post treatment (Frequency: $F_{(3,21)} = 0.08$, $p = 0.97$; Time: $F_{(3,21)} = 0.92$, $p = 0.45$; interaction: $F_{(9,63)} = 0.97$, $p = 0.47$) (Figure 25).

10.2.2: MEP onset latency. No changes in MEP onset latency were identified for either the MEPs recorded during volitional contraction (Frequency: $F_{(3,27)} = 1.14$, $p = 0.35$; Time: $F_{(3,27)} = 1.43$, $p = 0.26$; interaction: $F_{(9,81)} = 0.89$, $p = 0.54$) or MEPs recorded during volitional swallowing (Frequency: $F_{(3,21)} = 1.72$, $p = 0.19$; Time: $F_{(3,21)} = 0.46$, $p = 0.71$; interaction: $F_{(9,63)} = 0.58$, $p = 0.81$) (Appendices 8 & 9).

Figure 24:

Effect of stimulus frequency on MEP amplitude during volitional contraction (VC).

Error bars represent SD. Note. * $p < 0.05$

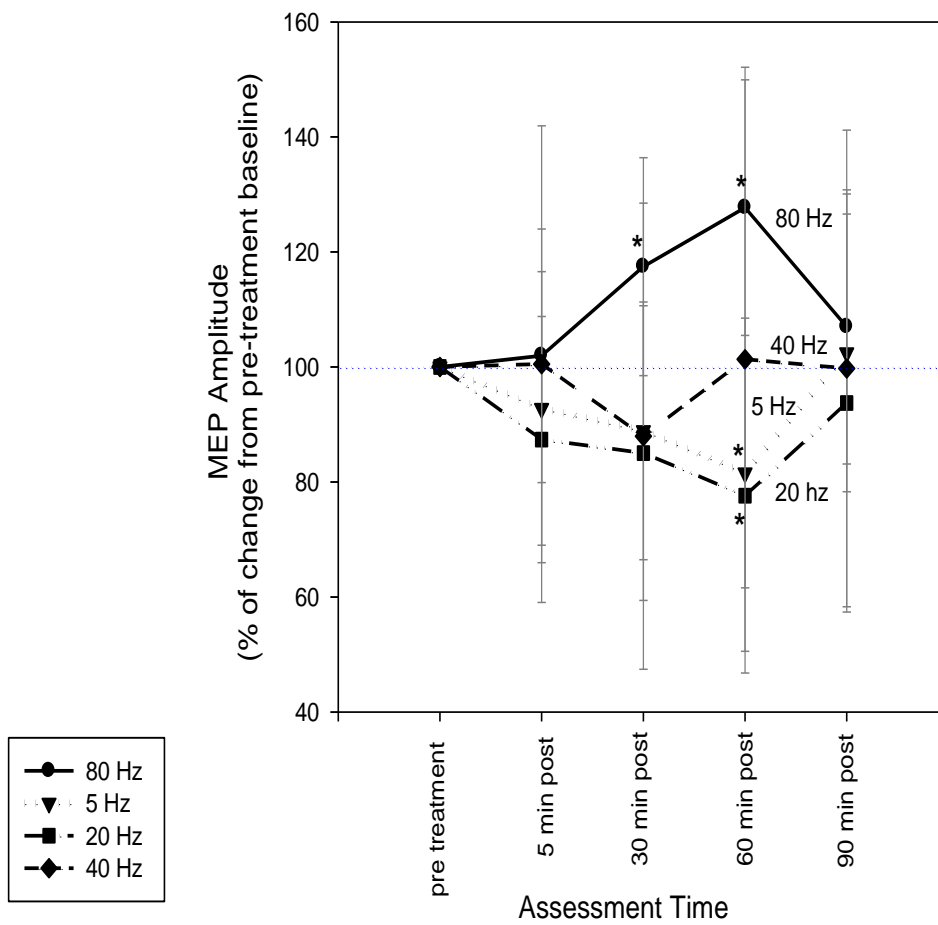
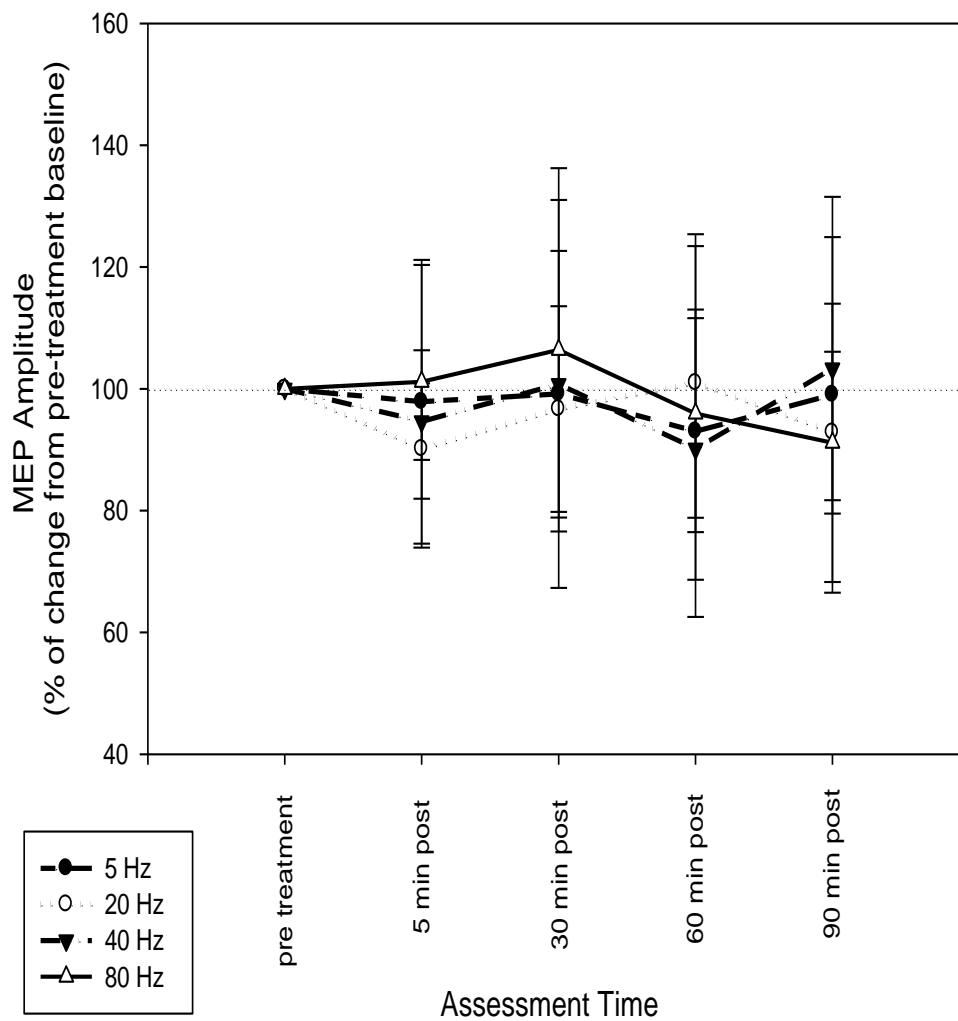


Figure 25:

Effect of stimulus frequency on MEP amplitude during volitional pharyngeal swallowing (VPS). Error bars represent SD. *Note.* * $p < 0.05$



10.3: Discussion

This investigation has documented long-lasting, frequency-specific effects of event-related NMES on submental MEP amplitude. Interestingly, these effects were observed only in MEPs elicited during volitional contraction and not in MEPs elicited during volitional swallowing. The largest significant changes in MEP amplitude occurred at 60 min post treatment after both excitatory (80 Hz) and inhibitory (5 Hz and 20 Hz) NMES.

The results of this study are in agreement with prior research that has documented frequency-specific changes in MEP amplitude in response to NMES treatment of muscles innervated by corticobulbar neural networks (Fraser et al., 2002; Power et al., 2004). However, the methodology employed in this study differed from the commonly used clinical application of NMES treatment and the acquisition of neurophysiological outcome measures in previous research. Here, NMES was provided in the task-related context of functional swallowing. Outcome measures were recorded in the task-related context of two different muscle contraction conditions and not when the target muscle was at rest. This allows interpretation of the frequency-specific effects of NMES on the excitability of corticobulbar projections during performance of these functional motor tasks.

No clear understanding exists as to how and why changes of corticobulbar or corticospinal excitability occur in response to NMES and how they relate to the frequency of the electrical stimulus. Previous research provides a framework for the interpretation and discussion of our results. Specifically, long-term potentiation (LTP) and depression (LTD) have been discussed as potential origins for altered synaptic plasticity (Fraser et al., 2002).

LTP is documented to result from coincident fast-frequency excitation of pre- and post-synaptic elements, which facilitates trans-synaptic chemical

transmission (Bliss & Gardner-Mewin, 1973). In contrast, LTD decreases synaptic efficiency and can be induced by low-frequency stimulation (Dudek & Bear, 1992) or mismatched pre- and post-synaptic activation (Markram et al., 1997). Bliss and Lomo (1973) were the first to describe the concept of LTP and LTD in the context of memory acquisition and learning in animals. A body of research is now available that describes LTP and LTD induction in the healthy and impaired human central nervous system following a variety of central and peripheral stimulation applications (Cooke & Bliss, 2006).

Of particular relevance for the interpretation of the results presented in this chapter may be the concept of interventional paired associative stimulation (IPAS) (Stefan et al., 2000). The authors reported LTP induction after IPAS, a technique of administering a peripheral electrical stimulus at an interval of 25 ms prior to a magnetic stimulus to the motor cortex. Excitability of the hand motor cortex increased after 90 paired stimulations, as determined by increased MEP amplitude recorded from the abductor pollicis brevis muscle in the thumb. Coincident activation of motor neurons by the ascending sensory stimulus and the descending volley evoked by TMS was thought to be the driving mechanism for the observed increase in cortical excitability. Similar results were reported by Ridding and Taylor (2001) who demonstrated increased MEP amplitude recorded from the first dorsal interosseous muscle after IPAS with an inter-stimulus interval of 25 ms. Conversely, Wolters et al. (2003) demonstrated that mismatching peripheral and cortical stimulation, by shortening inter-stimulus intervals, induced a reduction of cortical excitability.

It is possible that similar mechanisms of plasticity underlie the effects reported in this study, as exogenous electrical stimulation of the peripheral musculature coincided with the endogenous neural activation during volitional

swallowing. The frequency-specific changes in corticobulbar excitability likely relate to coincident (or mismatched) stimulation of the endogenously activated neural pathways. During swallowing, mainly fast-twitching muscle fibres are active (Korfage, Schueler, Brugman & Van Eijden, 2001; Stal, 1994). This type of muscle fibre is optimally stimulated with high-frequency stimulation (50-100Hz), whereas low-frequency stimulation (10 Hz) optimally mimics the natural innervation patterns of slow-twitch muscle fibres (Kit-Lan, 1992). It is therefore likely that the beneficial effects of high-frequency stimulation, as documented after 80 Hz NMES in this study, relate to the simultaneous activation of fast-twitch fibres by endogenously triggered muscle contraction and exogenous excitation through event-related NMES. Similarly, coincident afferent input to the sensorimotor cortex after IPAS of the pharyngeal musculature has previously also been demonstrated to induce facilitation of corticobulbar excitability (Gow, Hobson, Furlong & Hamdy, 2004). In contrast, low-frequency event-related NMES (5 Hz and 20 Hz in this study) may have induced a mismatch of exogenously induced electrical stimulation and endogenous muscle activation, resulting in LTD-like changes post treatment. It is interesting that 40 Hz NMES, at approximately halfway along the continuum of frequencies investigated here, neither facilitated nor inhibited corticobulbar excitability.

Further support for the hypothesis that LTP- and LTD-related processes induced the observed changes in corticobulbar excitability is the time course of 60 min over which the effects evolved. This time course is thought to relate to depolarisation of the post-synaptic cell in response to repetitive synaptic activation, which releases Mg^{2+} ions from blocking N-methyl-D-aspartate (NMDA) receptor gated ion-channels in the cell membrane. This consequently allows the rapid influx of Ca^{2+} ions into the post-synaptic cell, a process thought to increase synaptic strength for up to 2 hrs (Thompson et al. 1999; Malenka & Nicoll, 1999).

Comparable time courses have been reported for the effects on MEPs after altered peripheral input to the cranial muscles (Hamdy et al., 1998a; Fraser et al., 2002; Power et al., 2004), hand muscles (Stefan et al., 2000; Ridding et al., 2000) and arm muscles (Ziemann et al., 1998). A similar temporal pattern of stimulation-dependent changes in MEP amplitude has also been documented *during* prolonged stimulation (2 hrs) of the radial and ulnar nerves (McKay et al., 2002a). This research documented that MEP amplitude, recorded every 15 min during short breaks in stimulation, increased until 60 min post stimulation onset and remained elevated until 105 min post stimulation onset. The authors conclude that the time course of the induced change in the motor cortex is similar to that observed during volitional motor learning and LTP processes.

Interestingly, the excitatory and inhibitory effects documented in the current series of experiments were only observed in MEPs that were triggered by volitional contraction. MEPs triggered by the volitional swallowing condition remained unchanged after all NMES treatment trials. The question arises whether submental NMES activates sensorimotor areas that are relevant for the execution of volitional contraction only, rather than the execution of the pharyngeal phase of swallowing. This suggests that differences may exist in the neural networks governing the performance of these tasks and that only networks controlling volitional contraction are affected by event-related submental NMES. Paired with the observations of smaller submental MEP amplitude during volitional swallowing compared to volitional contraction (Chapter 9), the results of this study thus support the non-pyramidal cortical modulation model of swallowing neural control (p. 186). This will be discussed further in the Discussion chapter.

Previous research has documented a positive relationship between MEP amplitude recorded from pharyngeal muscles at rest, and swallowing function. After

facilitatory NMES of the pharyngeal musculature, a decrease in swallowing response time and aspiration was observed (Fraser et al., 2002). The results documented here seemingly contradict this finding, as one would expect MEPs recorded during volitional swallowing to be affected by NMES in a similar way. This was not documented to be the case. However, it is possible that increased excitability of M1 after NMES intervention, as documented by Fraser et al. in the resting muscle (2002) and here during volitional contraction, facilitated volitional movements in the oral phase of swallowing. Facilitation of oral motor control, in particular that related to posterior tongue movement and drop of base of tongue, may facilitate timely onset of swallowing. This would subsequently reduce swallowing onset time and risk of aspiration, as reported by Fraser et al. (2002). In contrast, the MEPs recorded during the reflexive phase of pharyngeal swallowing may more heavily rely on brainstem motor control, and not be affected as heavily by feedback from the primary motor cortex. In a similar context, Hamdy et al. (1998a) commented “it is possible that cortical inhibition may ensure that once brainstem CPG (central pattern generator) is activated, cortical discharge is suppressed, so that reflex swallowing can occur without interruption by other volitional commands to swallowing musculature” (Hamdy et al., 1997, p.865). This proposition was offered to explain absent facilitation of pharyngeal MEP amplitude in response to short-lasting (2.5 s) electrical stimulation delivered to the pharyngeal musculature, which decreased MEPs onset latency but did not alter MEP amplitude.

The question arises whether the changes in corticobulbar excitability documented in this study relate to changes in responsiveness at a cortical or brainstem level. As only MEPs recorded during volitional contraction showed altered amplitudes post treatment, it is likely that changes involved pyramidal corticobulbar pathways. If the excitability of neuron pools of the lower motor

neurons in the brainstem had been affected, then changes in MEP amplitude would likely have been observed during both the volitional contraction and volitional swallowing conditions. Additional support for this hypothesis can be gleaned from earlier research (Fraser et al., 2002), which reported that changes in MEP amplitude in response to peripheral NMES were greatest in MEPs recorded from the dominant hemisphere. The authors hypothesised that had changes occurred on a brainstem level, one might have expected MEPs recorded from both hemispheres to be affected to a similar degree. These considerations remain speculative and warrant further investigation.

As with any research employing human volunteers, this study is subject to a number of limitations. Within reasonable limits, only a restricted set of a large array of eligible stimulation frequencies have been evaluated. Further, the changes in corticobulbar excitability documented here remain to be linked to functional changes in swallowing performance. An evaluation of clinical relevance will be an essential prerequisite before any of the documented results can support the use of NMES in swallowing rehabilitation. It lies outside the scope of this research to answer these questions. Clearly, more research is needed to systematically investigate the neurophysiological underpinnings of the documented changes in corticobulbar excitability.

10.4: Conclusions

Altered sensory feedback through NMES of the submental muscle group changes corticobulbar excitability of the corresponding motor area when stimulation is paired with endogenous muscle activation. Sensory-induced effects are frequency-specific and evolve over a time course of approximately 60 min post treatment before returning to baseline at approximately 90 min. Task-dependent changes in

corticobulbar excitability observed in MEPs recorded during VC, but not the VPS, indicate that different neural networks may govern the motor execution of these tasks. A relationship to changes in measures of swallowing function remains to be established to support a clinical application of this treatment approach.

Chapter 11: Effect of Treatment Dose on the Excitability of Submental Corticobulbar Projections

Previous research has documented a relationship between the duration of NMES administered and the magnitude of the effect on MEP amplitude at other corticobulbar muscles (Fraser et al., 2002). Maximal changes in MEP amplitude occurred after non-event-related NMES of 10 min duration, whereas non-event-related NMES of 5 min or 20 min duration produced smaller post treatment changes. These data suggest that a window of maximal benefit may exist for dose of the electrical stimulation provided. Similarly, McKay, Ridding, Miles and Thompson (2002b) reported a different aspect of dose-dependency of the NMES-induced effects on the cortical representation of the first dorsal interosseus muscle. This group documented that repeated NMES sessions on consecutive days increased the duration of the excitatory effect of NMES for more than two days.

In light of these findings, optimal dose parameters were identified for event-related NMES of the submental musculature. In addition to the 60 repetitions of 4 s NMES stimulus trains used to identify optimal NMES frequency (see Chapter 10), two further dosages were evaluated in this study. Dosage was altered by decreasing the number of stimulus train repetitions (20 repetitions instead of 60 repetitions of a 4 s stimulus train) and by shortening the stimulus train duration (60 repetitions of a 1 s stimulus train instead of a 4 s stimulus train). Fewer repetitions of stimulus trains require participants, and ultimately patients, to perform fewer swallows to trigger NMES. Shorter stimulus intervals reduce the discomfort experienced during NMES. Together, these factors may lead to an easier transition of the event-related treatment

protocol from basic research into clinical rehabilitation practice, if beneficial results similar to the original treatment protocol can be achieved (Chapter 10). The following hypotheses were tested in this investigation:

Hypothesis 6A (research protocol 5): Sixty stimulus train repetitions will have a greater effect on MEP amplitude than 20 stimulus train repetitions.

Hypothesis 6B (research protocol 6): A stimulus train of 4 s duration will have a greater effect on MEP amplitude than stimulus trains of 1 s duration.

11.1: Methods

11.1.1: Participants. The same 10 research participants that were recruited for the investigation of frequency (Protocols 1 to 4, Chapter 10) participated in this study approximately 3 weeks later. Two participants of the original cohort withdrew from this study due to scheduling issues. Subsequently, two new participants were recruited into the study who completed the two dose comparison protocols (this Chapter) and, additionally, the 80 Hz event-related NMES protocol [optimal frequency (Chapter 10)]. This was done because the data of the latter were used for comparison in the subsequent statistical analyses. Mean age of the participant cohort enrolled in the investigation described in this chapter was 27.5 years (SD 3.5), including 6 female and 7 right-handed participants (Oldfield, 1971).

11.1.2: Data recording and NMES treatment. The procedures described in Chapter 10 were employed for this investigation. Participants attended two sessions of event-related NMES treatment, which were performed in counterbalanced order across participants. Each protocol varied from the optimal treatment parameters

identified in Chapter 10 by a single variable. Specifically, Protocol 5 provided fewer NMES stimulus train repetitions (20 repetitions instead of 60 repetitions) and Protocol 6 employed a shorter stimulus train duration (1 s instead of 4 s) at 60 stimulus train repetitions. All other stimulus parameters were identical to those employed in the prior protocol. The frequency of NMES was set to 80 Hz, as this frequency was identified previously as optimal for inducing facilitation of MEP amplitude. Blocks of 15 MEPs were recorded during each muscle contraction condition (volitional contraction or volitional swallowing) before NMES treatment (baseline) and 5 min, 30 min, 60 min and 90 min post treatment.

11.1.3: Data preparation and analysis. Statistical analyses were performed on the averaged data of each block of 15 MEP trials of each muscle contraction condition (VC and VPS) for each participant. Before calculating means, a repeated measures ANOVA was undertaken on the blocks of individual trials to identify potential trial effects. No significant trial effects were identified for any of the blocks of 15 trials (Appendices 6 & 7), except for the amplitude data of MEPs recorded during VPS, 5 min post treatment. As no general pattern of trial effects was identified across these investigations, mean amplitude and onset latency data of each set of 15 MEPs recorded during each muscle contraction condition (VC and VPS) at each assessment time (5 min, 30 min, 60 min and 90 min post treatment) were calculated. Subsequently, the percentage of change from pre treatment baseline was established for each post treatment assessment. Separate two-way repeated measures ANOVAs were performed on these relative values with the independent variables of “Dose” (number of stimulus train repetitions or duration of stimulus train) and “Time post treatment” (5 min, 30 min, 60 min, and 90 min) as repeated measures. ANOVAs excluded baseline data (100% of pre treatment performance), as these had

no variance. Data recorded for each dose were compared to the data recorded during the 80 Hz stimulation protocol of the previous study (Chapter 10). Statistical analyses were undertaken separately for amplitude and latency measures of each of the two muscle contraction conditions. Post-hoc paired-samples t-tests were performed to identify differences of post treatment measures compared to their pre-treatment baselines.

11.2 Results

11.2.1: Effect of dose on MEP amplitude (Protocol 5 and 6). For volitional contraction, a two-way repeated measures ANOVA of the MEP amplitude data revealed a significant effect of Time and a significant interaction between the Number of Repetitions and Time (Repetitions: $F_{(1,9)} = 1.03$, $p = 0.336$; Time: $F_{(3,27)} = 3.32$, $p = 0.035$; interaction: $F_{(3,27)} = 3.33$, $p = 0.035$) indicating that the two treatment paradigms affect cortical excitability differentially across time (Figure 26). A significant quadratic trend above pre treatment baseline was observed for post treatment effects after 60 repetitions of 4 sec stimulus trains ($p = 0.006$), with maximal increase in MEP amplitude occurring at 60 min post treatment, before returning toward baseline at 90 min post treatment. In contrast, no significant trends were observed after NMES provided at only 20 repetitions. Two-tailed paired-samples t-tests revealed that after 20 repetitions there were no significant changes in MEP amplitude from pre-treatment baseline.

Further, a repeated measures ANOVA revealed a significant main effect of Time and a significant interaction between Time and Stimulus Train Duration (Duration: $F_{(1,9)} = 3.45$, $p = 0.096$; Time: $F_{(3,27)} = 4.1$, $p = 0.017$; interaction: $F_{(3,27)} = 2.98$, $p = 0.049$) indicating that the two treatment paradigms evaluated in Protocol 6 affect cortical excitability differentially across time (Figure 26). A significant linear

downward trend was observed after 80 Hz NMES provided at 1 s stimulus trains ($p = 0.02$), whereas a significant quadratic trend above baseline was observed after 80 Hz NMES administering 4 s stimulus trains ($p = 0.006$) (Figure 26).

For volitional swallowing, no significant differences between treatment protocols were observed after 60 or 20 repetitions of a 4 sec stimulus train (Repetitions: $F_{(1,7)} = 0.89$, $p = 0.774$; Time: $F_{(3,21)} = 0.678$, $p = 0.575$; interaction: $F_{(3,21)} = 1.45$, $p = 0.256$). Similarly, no significant differences between treatment protocols were observed for MEP amplitude recorded during volitional swallowing after 60 repetitions of a 1 sec or a 4 sec stimulus train (Duration: $F_{(1,7)} = 0.073$, $p = 0.795$; Time: $F_{(3,21)} = 0.822$, $p = 0.5$; interaction: $F_{(3,21)} = 0.654$, $p = 0.59$).

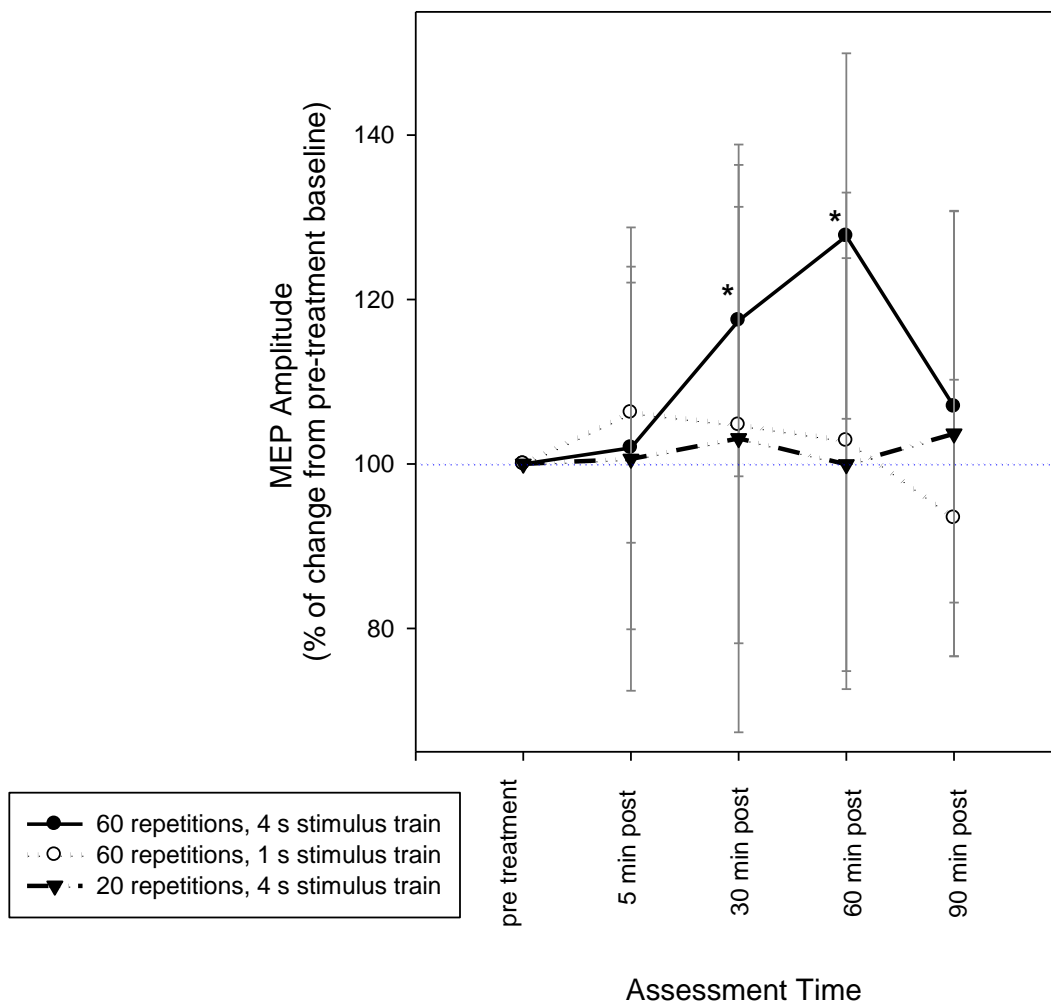
11.2.2: Effect of dose (Protocols 5 and 6) on MEP onset latency. No significant changes in MEP onset latency were observed in any of the dose comparisons for either the volitional contraction or the volitional swallowing tasks (Appendices 8 & 9).

Figure 26.

Effect of NMES dose on MEP amplitude during volitional contraction (VC). *Note.*

Significant changes only occurred after 60 repetitions of NMES stimulus trains.

Error bars represent SD. * $p < 0.05$.



11.3: Discussion

This study identified the effects of treatment dose of event-related NMES on MEP amplitude and onset latency recorded from the submental muscle group. Significant differences in MEP facilitation were documented after 80 Hz event-related NMES between protocols employing 20 or 60 stimulus train repetitions and between protocols employing stimulus trains lasting 1 or 4 sec. Specifically, changes in MEP amplitude only occurred after the treatment trial that employed the longer stimulus train duration and the greatest number of repetitions.

This finding is in agreement with the initial hypotheses that fewer stimulus train repetitions would produce smaller effects than NMES provided at a greater number of stimulus train repetitions or longer stimulus trains. It is likely that the overall greater sensorimotor stimulation administered during the original 80 Hz NMES treatment protocol (60 repetitions of a 4 s stimulus train) accounts for these differences. Further research is warranted to evaluate whether even greater effects can be induced by greater stimulus train repetitions or longer stimulus trains.

In order to gain neurophysiological benefits from event-related NMES, research participants had to perform a relatively large number of swallows. This limits the clinical applicability of event-related NMES to patient groups that have retained a certain degree of swallowing function. However, before event-related NMES can be applied as a rehabilitative tool, evaluation of which patient groups will benefit most from this treatment approach will need to be undertaken. Further, it will be of interest to establish whether non-event-related NMES will provide similar beneficial effects as event-related NMES. If the latter was found to be the case, then patient groups that have difficulty initiating a volitional swallow to trigger NMES might benefit from this treatment approach. Clinical and basic research is warranted to answer these questions.

11.4 Conclusions

The excitatory effects induced by 80 Hz event-related NMES are dose-dependent. Significant increases in MEP amplitude can be induced by 60 swallow-triggered repetitions of 4 s stimulus trains. Facilitatory effects could be observed in MEPs recorded during volitional pre-activation of the target muscles, but were not evident in MEP recorded during volitional swallowing.

PART VI

Chapter 12: Replication of Treatment Effects After 80 Hz NMES

Replication of research results is an important cornerstone in confirming the validity of research findings and strengthening their interpretation. Ioannidis (2005) demonstrated through statistical calculations of positive predictive values that most reported research findings are, in fact, false due to factors such as low statistical power, inadequate research and analysis designs, chance variability or bias. Moonesinghe, Khoury and Janssens (2007) extended these calculations and showed that, on the other side, the positive predictive value of research findings being true increases when replication of research paradigms yields the same statistically significant results.

The pattern of change documented after 80 Hz NMES in this research programme is supported by similar, previously reported, findings. In particular, the development of post treatment changes was frequency-specific and followed a similar time course as reported by other researchers (Fraser et al., 2002; Power et al., 2004). However, previous research employed different, albeit similar, methodologies and can therefore only indirectly support the findings of the present research programme. Replication of the results documented in this research programme using identical methods will provide stronger support for the validity of these findings. Due to the particular interest in stimulus parameters that increase cortical excitability, we sought to replicate the effects of the 80 Hz NMES treatment paradigm. Sample size was increased from 10 to 15 participants in order to enhance statistical sensitivity in detecting smaller effect sizes. The following hypothesis was tested:

Hypothesis 7: Similar effects as those documented previously (Chapter 10) will be observed in the second cohort undergoing event-related NMES at optimal stimulus parameters.

12.1: Methods

12.1.1: Participants. Nineteen healthy research participants were initially screened for inclusion into this study [mean age 26.4, SD 6.2 years, 17 right-handed (Oldfield, 1971)]. In four participants, no discernable MEPs could be recorded from either hemisphere; therefore these participants were excluded from further data collection. Thus, a total of 15 healthy participants [mean age 27.1 years, SD 7.1 years, 14 right-handed (Oldfield, 1971)] were recruited into the study. Participants provided written informed consent and expressed full comprehension of the research procedures. Participants had no medical history or current symptoms of dysphagia and reported no neurological impairment and no drug use that would potentially affect their swallowing or neurological function. This study received ethical approval from the appropriate Human Ethics Review Committee.

12.1.2: Research protocol (7). Identical methods were employed as described in Chapter 10. Event-related NMES was provided through sEMG electrodes mounted over the submental muscle group at midline, with a stimulus train duration of 4 s and a stimulus frequency of 80 Hz. Surface EMG recordings of thyrohyoid activity triggered NMES stimulus trains during 60 normal swallows with rest periods of at least 12 s in between swallows. Motor evoked potentials were recorded from the submental muscle group using the same electrodes that provided NMES, and measurements were made pre-treatment and at 5 min, 30 min, 60 min and 90 min post treatment during volitional contraction and volitional swallowing.

12.1.3: Data preparation and analysis. Statistical analyses were performed on the averaged data of each block of 15 MEP trials of each muscle contraction condition (VC and VPS) for each participant. Before calculating means, a repeated measures ANOVA was undertaken on the blocks of individual trials to identify potential trial effects. No significant trial effects were identified for any of the blocks of 15 trials (Appendices 6 & 7), except for the onset latency data of MEPs recorded during VC, 5 min post treatment. As no general pattern of trial effects was identified across this investigation, mean amplitude and onset latency data of each set of 15 MEPs recorded during each muscle contraction condition (VC and VPS) at each assessment time (baseline and at 5 min, 30 min, 60 min and 90 min post treatment) were calculated. Subsequently, the percentage of change from pre treatment baseline was established for each post treatment assessment. Two-tailed paired samples t-tests were performed on these relative data to compare changes of MEP amplitude and onset latency at each post treatment assessment (5 min, 30 min, 60 min and 90 min) to pre-treatment baseline. These analyses were undertaken separately for amplitude and latency measures recorded during each of the two muscle contraction conditions (volitional contraction and volitional swallowing). Additionally, the same analyses were performed on the pooled data of the two participant cohorts.

12.2: Results

12.2.1: MEP amplitude. For volitional contraction, two-tailed paired-samples t-tests revealed a significant increase in MEP amplitude at 60 min post treatment ($t_{(14)} = 2.637$, $p = 0.02$). The effect size of this comparison was $d = 0.98$. As in the initial investigation (Chapter 10), a significant quadratic trend above

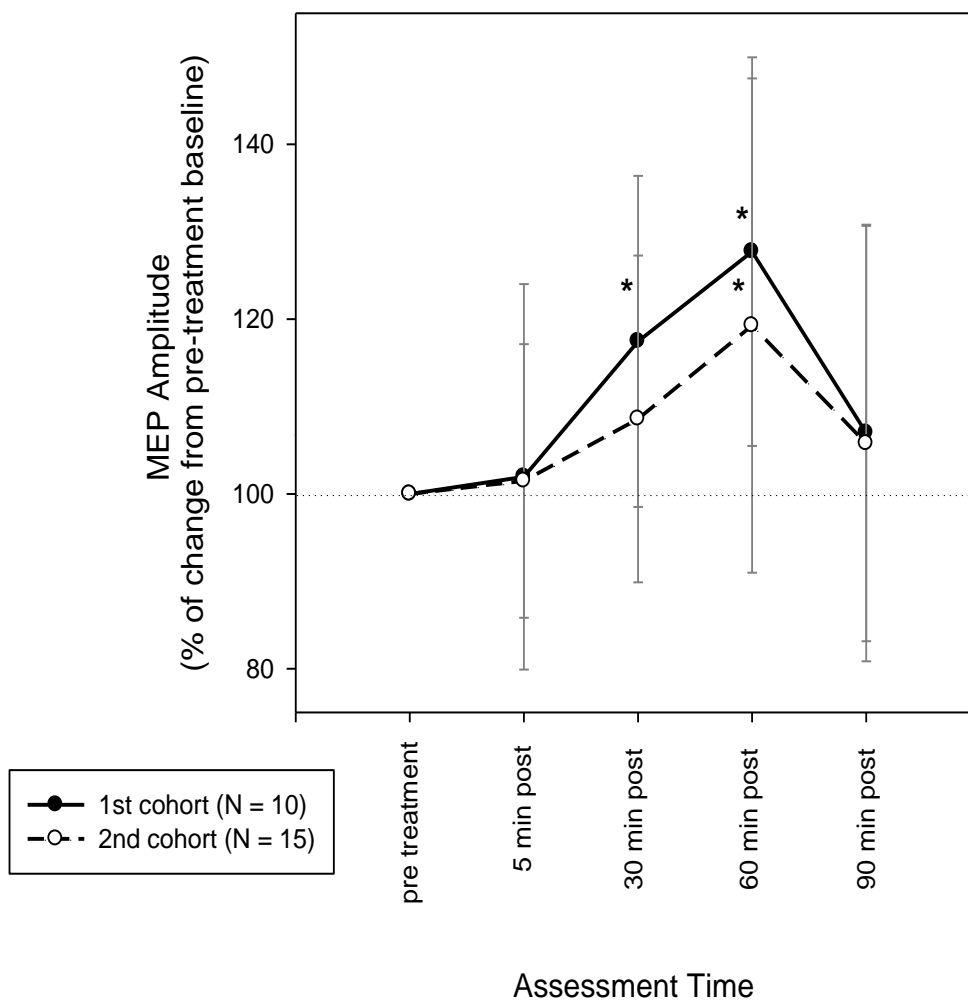
baseline was observed ($p = 0.005$). As treatment protocols were identical between the two participant cohorts, data of both participant groups were pooled. Two-tailed paired-samples t-tests of the combined MEP amplitude data recorded during VC revealed a significant increase from baseline at 30 min ($t_{(24)} = 3.2$, $p = 0.004$) and 60 min post treatment ($t_{(24)} = 4.37$, $p < 0.001$). The effect sizes of these comparisons were $d = 0.906$ and $d = 1.24$ at 30 min and 60 min post treatment, respectively. Figure 27 presents changes in MEP amplitude relative to pre-treatment baseline for both the original 80 Hz NMES protocol (Chapter 10) and the replication study. Note that sample sizes differed in that 10 research participants were included in the original investigation and 15 research participants were included in the second investigation.

In contrast to MEPs recorded during volitional contraction, no significant changes in MEP amplitude recorded during the volitional swallowing condition were observed at any post treatment assessment. This was also the case when the data of both participant groups were pooled.

12.2.2: MEP onset latency. Two-tailed paired-samples t-test of the MEP onset latency data recorded during volitional contraction comparing the changes of MEP onset latency at each post treatment assessment (5 min, 30 min, 60 min and 90 min post treatment) to pre-treatment baseline revealed no significant changes in MEP onset latency at any post treatment assessment. Similarly, no significant changes in MEP onset latencies recorded during the volitional swallowing condition were observed at any post treatment assessment (Appendices 8 & 9).

Figure 27.

Replication of 80 Hz NMES treatment trial - effects on MEP amplitude during volitional contraction (VC). Error bars represent SD. *Note.* * $p < 0.05$.



12.3 Discussion

Replication of the 80 Hz NMES treatment protocol produced very similar findings to those documented in the original investigation in a larger participant cohort. In particular, the excitatory effect on MEP amplitude recorded during VC

demonstrated a large degree of stability as it followed the same time course in both investigations.

Interestingly, the overall effect sizes of the post treatment changes at 30 min and 60 min were smaller than in the original investigation. In fact, at 30 min post treatment, the observed changes were not significantly different, although a similar trend was observed in comparison to the original study with maximal effects at 60 min post treatment. No obvious outliers in the data set were identified to explain this small discrepancy; therefore it is likely that the results represent an overall variability in the magnitude of the post treatment effect in different cohorts. The overall pattern of change, however, was very similar between the two groups.

In agreement with the first investigation, no changes were observed in MEP amplitudes recorded during the VPS condition. As discussed in Chapter 10, changes in corticobulbar excitability in response to event-related NMES may not be observable when MEPs are recorded during pharyngeal swallowing. This may indicate differences in the neural networks that govern the motor execution of these tasks.

12.4 Conclusions

Facilitation of the excitability of corticobulbar projections to the submental muscle group is a replicable and stable effect in response to 80 Hz event-related NMES. This effect is measurable in the amplitude of MEPs recorded during volitional pre-activation of the muscle group. A relationship between facilitated MEP amplitude and contractile function of the stimulated muscle group remains to be established.

Chapter 13: Comparison of the Effects of Event-related and Non-event-related NMES

Previous investigations undertaken in the framework of this research programme have established optimal stimulus frequency and treatment dose for event-related NMES of the submental muscle group. The role of the task context during which NMES is administered, however, still remains unknown. As outlined in the literature review (Chapter 3), discussion exists in various areas of rehabilitation medicine around the question whether NMES provided in a task-related context (event-related NMES) is superior to NMES administered when the target muscle is at rest. Early evidence for this hypothesis exists in the area of physical rehabilitation medicine (DeKroon et al., 2005); however, no clear relationship has been established between the additional cognitive involvement required during event-related NMES and improved effectiveness of this treatment approach. Conceptually, it is plausible that time-locked endogenous and exogenous neuromuscular excitation may provide superior facilitation of the sensorimotor system than exogenous stimulation alone, as sensory and motor pathways are activated concomitantly. For example, it has been documented that traditional voluntary exercise of the biceps brachii muscle of 24 healthy research participants resulted in significantly greater increase in muscle strength than non-event-related NMES. In fact, strength gains after non-event-related NMES treatment of the biceps brachii were not significantly different from those after no training at all (Holcomb, 2006).

In swallowing rehabilitation, no previous research has directly compared the effects of event-related and non-event-related NMES on neurophysiological or functional outcome measures. In most previous investigations, non-event-related

NMES was administered to healthy or swallowing impaired participant cohorts and only one clinical study has evaluated the effects of a long-term event-related NMES treatment protocol in a group of individuals with dysphagia (Leelamanit et al., 2002). A number of studies have employed the non-event-related treatment protocol promoted as VitalStim™ therapy, during which non-event-related NMES is administered for 1 hr continuously. Conflicting results have been reported in regards to the efficacy of this approach (refer to Chapter 3).

Due to the discrepant findings reported in earlier research, and the lack of systematic study of this issue in swallowing rehabilitation, the current study compared effects induced by event-related and non-event-related NMES. Based on evidence in other rehabilitation paradigms, it was predicted that event-related NMES produces greater effects than non-event-related NMES. This chapter describes an investigation to (a) compare the effects of 80 Hz event-related NMES (Chapter 12) to those induced by a non-event-related NMES protocol employing identical treatment parameters and to (b) compare the effects induced by that non-event-related NMES protocol to those induced by 1 hr of continuous non-event-related NMES. The following hypotheses were tested:

Hypothesis 8: Non-event-related NMES, administered at identical stimulus parameters as event-related NMES, will produce smaller changes in post-treatment outcome measures than event-related NMES.

Hypothesis 9: Sixty minutes of non-event-related NMES will produce increased MEP amplitude and no changes in onset latency. These changes will be greater than those administered during non-event-related NMES employing the optimal parameters established previously for event-related NMES.

13.1: Methods

13.1.1: Participants. The same research participants that were investigated in the replication study described in Chapter 12 were included in these investigations (15 healthy individuals, mean age 27.1 years, SD 7.1 years, 14 right-handed (Oldfield, 1971)]. Participants gave written informed consent and expressed full comprehension of the research procedures. Participants had no medical history or current symptoms of dysphagia and reported no neurological impairment and no drug use that would potentially affect their swallowing or neurological function. This study received ethical approval from the appropriate Human Ethics Review Committee.

13.1.2: Data acquisition. Data for the two non-event-related protocols were collected in independent sessions, at least three days apart. Two submental surface electrodes and the reference electrode at the mandibular prominence at the base of the vertical ramus were mounted for these studies. After the trigger threshold had been determined and the optimal scalp location for eliciting MEPs had been identified, 15 MEPs were recorded during both the VC and VPS contraction conditions as baseline measures. Then, one of two non-event-related treatment protocols (Protocol 8 or 9) was administered in counterbalanced order across participants.

13.1.3: Non-event-related NMES (Protocol 8). Subsequent to baseline assessment, non-event-related NMES was administered using the following NMES parameters:

- stimulus train duration: 4 s
- pulse characteristics: 200 μ s square pulse

- stimulation intensity: 75% of the individual's pain threshold
- repetitions: 60 stimuli trains (each triggered *automatically*)
- stimulus frequency: 80 Hz

These parameters are identical to those provided during the previous event-related NMES paradigm in the same participants, except that stimulus trains were triggered automatically, and not from swallowing-related sEMG. Non-event-related NMES was provided with periods of 12 s in between stimulus trains in order to match the rest period that was mandatory during the event-related NMES paradigm. Subsequent to the treatment period, 15 MEPs were recorded from the submental musculature during each of the two muscle contraction conditions. Further sets of 15 MEPs per condition were recorded at 30 min, 60 min and 90 min post treatment.

13.1.4: One Hr Continuous NMES (Protocol 9). Subsequent to baseline assessment, continuous, non-event-related NMES was administered using the following NMES parameters:

- stimulus train duration: 1 hr, administered continuously
- pulse characteristics: 200 μ s square pulse
- stimulation intensity: 75% of the individual's pain threshold
- stimulation frequency: 80 Hz

Subsequent to the treatment period, 15 MEPs were recorded from the submental musculature during each of the two muscle contraction conditions. Further sets of 15 MEPs per condition were recorded at 30 min, 60 min and 90 min post treatment.

13.1.5: Data preparation and analysis. Before collapsing the data sets from individual trials to mean data for each participant, a repeated measures ANOVA was

performed on the individual trials to identify potential trial effects. No such effects were identified for amplitude or latency data in either condition (see Appendices 6 & 7). To control for inter-individual variability, MEP amplitude and latency measures were expressed as a percentage of change from baseline of at each post treatment assessment (5 min, 30 min, 60 min and 90 min).

Two comparisons were undertaken in this investigation. One, the effects induced by the 80 Hz event-related NMES protocol (Protocol 7, Chapter 12) were compared to those induced by non-event-related NMES (Protocol 8, this chapter). Two, the effects induced by non-event-related NMES (Protocol 8) were compared to those induced by continuous NMES (Protocol 9). Event-related NMES was not compared to continuous NMES, as stimulation paradigms varied by more than one variable (event context and stimulus duration). Two-way repeated measures ANOVAs were performed on the respective data with the variables “Protocol” and “Time of assessment” in order to identify the effects of these variables and their interaction on MEP measures. Two-tailed paired-samples t-tests were performed to identify post treatment changes from baseline at each assessment time. Analyses were performed separately for amplitude and latency measures of each of the two muscle contraction conditions.

13.2: Results

13.2.1: Event-related versus non-event-related NMES - MEP amplitude.

Two-way repeated measures ANOVA of the amplitude data recorded during VC showed a significant main effect of Time (Time: $F_{(3, 42)} = 4.3$, $p = 0.01$; Protocol: $F_{(1, 14)} = 1.4$, $p = 0.26$). Although the Time by Protocol interaction was not significant ($F_{(3, 42)} = 1.7$, $p = 0.19$), significant quadratic trends were observed after both types of NMES, with changes in MEP amplitude occurring above pre-treatment

baseline after event-related NMES ($p = 0.005$), and below pre-treatment baseline after non-event-related NMES ($p = 0.028$). Subsequent two-tailed paired-samples t -tests revealed that, in contrast to the increase at 60 min after event-related NMES, non-event-related NMES produced no significant changes from baseline at any post treatment assessment (Table 10). Figure 28 illustrates mean MEP amplitudes recorded during volitional contraction for all treatment protocols across time. Note that significant changes from pre-treatment baseline only occurred after the event-related NMES treatment.

Two-way repeated measures ANOVA revealed no significant main effects or interactions when comparing MEPs recorded during volitional swallowing (Protocol: $F_{(1,9)} = 0.23$, $p = 0.64$; Time: $F_{(3,27)} = 0.3$, $p = 0.83$; Interaction: $F_{(3,27)} = 0.27$, $p = 0.85$). No significant changes from baseline were observed at any assessment time after non-event-related NMES (Table 10).

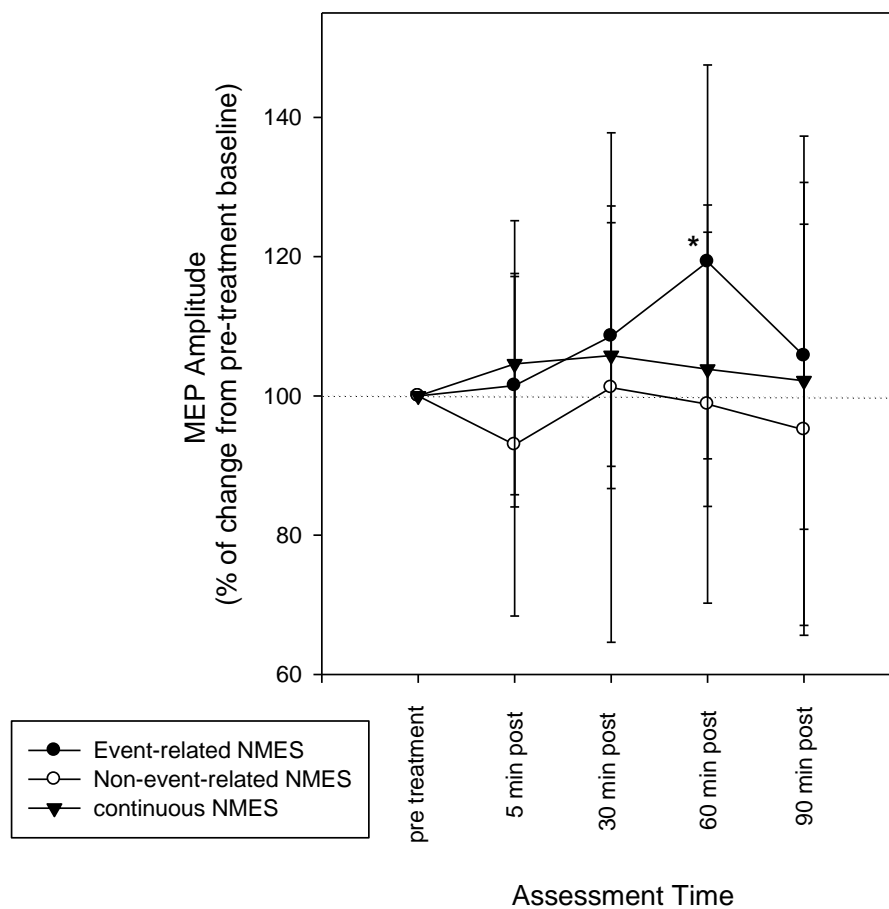
13.2.2: Non-event-related NMES versus 1 hr continuous non-event-related NMES - MEP amplitude. Two-way repeated measures ANOVA comparing MEP amplitude recorded during volitional contraction showed no significant main effects or interactions (Protocol: $F_{(1,14)} = 0.54$, $p = 0.48$; Time: $F_{(3, 42)} = 0.64$, $p = 0.59$; Interaction: $F_{(3, 42)} = 0.304$, $p = 0.82$) (Figure 28). No significant trends were observed after continuous NMES. Two-tailed paired-samples t -tests revealed no significant changes from baseline measures of MEP amplitudes recorded during volitional contraction at any post treatment assessment (Table 10).

Two-way repeated measures ANOVA revealed no significant main effects or interactions when comparing MEPs recorded during volitional swallowing (Protocol: $F_{(1,9)} = 0.55$, $p = 0.48$; Time: $F_{(3,27)} = 0.67$, $p = 0.58$; Interaction: $F_{(3,27)} =$

0.88, $p = 0.46$). No significant changes from baseline were observed at any assessment time after non-event-related NMES (Table 10).

Figure 28.

Effect on MEP amplitude, recorded during volitional contraction (VC), relative to pre-treatment baseline, in response to 80 Hz NMES treatment trials administered in (a) an event-related context, (b) non-event-related context (at rest) and (c) continuously for 1 hr. Error bars represent SD. *Note.* Significant changes from pre-treatment baseline only occurred after event-related NMES treatment. * denotes $p < 0.05$.



13.2.3: Effects of treatment protocols 8 and 9 on MEP onset latency. No significant main effects or interactions were found when comparing MEP onset latencies after event-related and non-event-related NMES treatment protocols during volitional contraction (Protocol: $F_{(1,14)} = 0.1$, $p = 0.98$; Time: $F_{(3,42)} = 1.03$, $p = 0.39$; Interaction: $F_{(3,42)} = 1.2$, $p = 0.28$) or during volitional swallowing (Protocol: $F_{(1,9)} = 0.5$, $p = 0.82$; Time: $F_{(3,27)} = 0.051$, $p = 0.98$; Interaction: $F_{(3,27)} = 2.03$, $p = 0.18$). No significant changes in MEP onset latency were identified post treatment for either the MEPs recorded during volitional contraction or during volitional swallowing (Table 11) (Appendices 8 & 9).

No significant main effects or interactions were found when comparing MEP onset latencies after continuous and non-event-related NMES treatment protocols during volitional swallowing (Protocol: $F_{(1,14)} = 2.73$, $p = 0.12$; Time of Assessment: $F_{(3,42)} = 1.13$, $p = 0.35$; Interaction: $F_{(3,42)} = 2.81$, $p = 0.051$) or during volitional swallowing (Protocol: $F_{(1,9)} = 0.51$, $p = 0.49$; Time: $F_{(3,27)} = 0.88$, $p = 0.47$; Interaction: $F_{(3,27)} = 0.70$, $p = 0.57$) (Appendices 8 & 9). Two-tailed paired-samples t-tests revealed a significant change only in MEP onset latency 90 min post treatment (continuous NMES) during the volitional contraction condition (Table 11).

Table 10.

Post treatment effects of event-related NMES and non-event-related NMES on MEP amplitudes. Means and SD are displayed.

	Condition	Baseline	5 min post	30 min post	60 min post	90 min post
Event-related NMES	VC	698.46 (287.9)	722.47 (384.9)	742.34 (306.8)	809.08 (354.6)	721.3 (334.1)
	VPS	443.32 (172.5)	459.26 (197.0)	444.67 (174.6)	443.76 (187.7)	443.08 (169.3)
Non-event-related NMES	VC	874.72 (444.6)	789.8 (389.8)	841.83 (399.4)	835.61 (413.6)	810.14 (394.6)
	VPS	566.07 (282.6)	533.82 (272.1)	550.03 (270.3)	520.31 (238.7)	561.88 (289.1)
Continuous NMES	VC	878.7 (474.5)	871.56 (419.6)	909.83 (495.0)	865.1 (429.1)	846.36 (462.8)
	VPS	614.5 (257.9)	634.4 (310.0)	664.62 (303.6)	650.63 (279.6)	580.22 (210.3)

Note. Significant differences ($p < 0.05$) from pre-treatment baseline are displayed in bold.

Table 11.

Post treatment effects of event-related NMES and non-event-related NMES on MEP onset latencies. Means and SD are displayed.

	Condition	Baseline	5 min post	30 min post	60 min post	90 min post
Event-related NMES	VC	8.4 (0.98)	8.3 (0.95)	8.4 (1.07)	8.3 (1.09)	8.4 (1.09)
	VPS	8.6 (1.1)	8.6 (1.1)	8.7 (1.1)	8.6 (1.2)	8.6 (1.2)
Non-event-related NMES	VC	8.1 (0.89)	8.2 (0.93)	8.2 (0.82)	8.0 (0.89)	8.0 (0.74)
	VPS	8.4 (1.2)	8.4 (1.03)	8.3 (1.02)	8.3 (0.97)	8.4 (1.1)
Continuous NMES	VC	8.2 (1.09)	8.4 (1.2)	8.3 (1.1)	8.3 (1.2)	8.4 (1.2)
	VPS	8.3 (1.2)	8.4 (1.06)	8.3 (1.1)	8.2 (1.1)	8.3 (1.05)

Note. Significant differences ($p < 0.05$) from pre-treatment baseline are displayed in bold.

13.3 Discussion

This investigation compared the effects of event-related NMES to those induced by non-event-related NMES treatment trials. Non-event-related NMES did not produce changes in corticobulbar excitability during either volitional contraction or volitional swallowing, even when non-event-related NMES was administered for 1 hr continuously. Comparison of the effects induced by event-related and non-event-related NMES showed MEP amplitude increases only after event-related NMES. The effects induced by 1 hr continuous NMES did not differ to those induced by the non-event-related NMES treatment trial.

These findings are in agreement with the initial hypotheses that changes in corticobulbar excitability differ depending on the type of NMES, in particular the

functional context during which NMES is administered. The comparison of event-related and non-event-related NMES revealed that MEP amplitudes varied across time.

Clinically, it is of interest to evaluate which intervention induces superior neurophysiological treatment effects. While statistical analyses did not identify a significant effect of treatment type, event-related NMES produced more favourable results than the non-event-related NMES protocol, in that post treatment changes in MEP amplitudes occurred above pre-treatment baseline. In fact, comparing MEP amplitudes recorded at each post treatment assessment to pre-treatment baseline revealed that significant increases in corticobulbar excitability occurred only after event-related NMES.

In light of the considerations offered in regards to LTP induction during event-related NMES (as discussed in more detail in Chapter 10), it is plausible that non-event-related NMES did not affect MEP amplitude because exogenously administered NMES did not occur concomitantly with endogenous muscle activation (Bliss & Gardner-Mewin, 1973).

Interestingly, the effects induced by continuous non-event-related NMES did not differ from those induced by non-event-related NMES, even though a substantially greater amount of sensorimotor stimulation was administered during this protocol. The only significant effect found after continuous NMES was a slight (2%) increase in MEP onset latency 90 min post treatment in MEPs that were recorded during the volitional contraction condition. This finding is somewhat surprising, as no other effects on MEP onset latency have been documented for any of the comparisons undertaken in this research programme. One might argue that the effects of muscle fatigue after 1 hr of continuous sensorimotor stimulation are responsible for this increase in MEP onset latency. However, the effects of fatigue

would be expected to occur immediately after the treatment trial and not 90 min after conclusion of stimulation. No outliers were identified in the data set. The neurophysiological underpinnings of this isolated effect on MEP onset latency therefore warrant further investigation.

The effects presented here are in contrast to those reported by earlier studies, which have documented changes in MEP amplitude after 10 min of non-event-related NMES of the pharyngeal (Fraser et al., 2002) or faucial pillar (Power et al., 2004) musculature. It is possible that short stimulus trains of 4 s duration administered every 12 s do not provide sufficient peripheral input to alter the excitability of corticobulbar projections. On the other hand, 1 hr of continuous NMES may exceed what is optimally required to increase corticobulbar excitability. These considerations are supported by the findings reported by Fraser et al. (2002), who documented that outside a window of optimal stimulus duration (10 min), no effects on corticobulbar excitability were observed. Future research is indicated to identify whether non-event-related NMES administered for different periods of time than in the current investigation yield neurophysiological benefits.

As reported in the preceding investigations of this research programme, no effects on MEP amplitudes were observed when the excitability of corticobulbar projections was tested during volitional swallowing. These results will be discussed in more detail and in the context of all results of this research programme in the discussion chapter (Chapter 14).

13.4: Conclusions

Strong indications exist that event-related NMES is superior to non-event-related NMES in increasing the excitability of corticobulbar projections, when these are tested during volitional muscle pre-activation. This finding is in agreement with

conceptual considerations that coincident endogenous excitation and exogenously administered sensorimotor stimulation induce superior effects than sensorimotor stimulation outside a functional context.

Part VII

Chapter 14: Discussion

This research programme provides new information about the effects of event-related and non-event-related NMES on the excitability of corticobulbar projections to the submental muscle group. Frequency-specific changes in corticobulbar excitability, reflected in increased or decreased MEP amplitude, were identified in response to event-related NMES, with a distinct differentiation between high-frequency NMES inducing excitatory effects and low-frequency NMES inducing inhibitory effects. Further, the magnitude of the induced changes was positively related to the dose of event-related NMES administered. In contrast, non-event-related NMES did not induce changes in corticobulbar excitability, whether applied using the same treatment parameters as the event-related NMES or when administered continuously for 1 hr. Elicitation of MEPs during task-related muscle pre-activation, that is, volitional contraction (VC) and volitional pharyngeal swallowing (VPS) was documented to be a reliable measure. Mean MEP amplitudes and onset latencies were stable across the duration of a recording session (2 hr) and across multiple, independent recording sessions. Repeated volitional swallowing did not affect MEP amplitude and latency measures. Comparisons of MEP measures recorded during two voluntary (VC and VPS) and one reflexive muscle pre-activation conditions (reflexive pharyngeal swallowing, RPS) revealed that MEPs were largest and detected most consistently during voluntary pre-activation, were less frequently detected and smaller in amplitude during the pharyngeal phase of volitional swallowing and were infrequently detected during pre-activation by reflexive swallowing. Implications derived from these findings for the application of

NMES in swallowing rehabilitation practices and our understanding of the neural control of swallowing are discussed in this chapter.

14.1: Methodological considerations

Previous research evaluating MEPs recorded from the masseter muscle has indicated that muscle pre-activation is necessary in order to record discernable MEPs (Benecke et al., 1988; Cruccu et al., 1990). Paired with the conceptual consideration that MEPs recorded in a functional context provide information about the magnitude of corticobulbar excitability during task performance, this research programme investigated the effects of NMES on submental MEPs recorded during muscle pre-activation. As the submental muscle group is involved in the oral (jaw movement) and pharyngeal phases of swallowing (hyo-laryngeal elevation), early exploratory work on research methods investigated whether volitional contraction or volitional swallowing would be most suitable for pre-activating the submental musculature. Interestingly, in many participants, MEPs appeared significantly larger during the volitional contraction condition, and they were smaller or not always measurable during the volitional pharyngeal swallowing condition. As the TMS trigger threshold was set to an identical value during both muscle contraction conditions, it was of interest to investigate whether differences exist in the underlying level of corticobulbar facilitation during these tasks. Therefore, a systematic, expanded evaluation of this phenomenon was undertaken, which also included a reflexive swallowing muscle pre-activation condition. As discussed in Chapter 9, this investigation revealed distinct differences in the measurement of submental MEPs during the pre-activation tasks. MEPs facilitated by volitional contraction were significantly larger than those recorded during volitional pharyngeal swallowing and were measurable in most of the studied research participants (22 of 35 participants). In contrast, MEPs facilitated by reflexive

swallowing only occurred in the minority of participants (6 of 19 participants) (Chapter 9). Due to these findings, the exploratory investigation evolved into a secondary focus of this research programme. As clear differences were observed between the voluntary contraction and volitional swallowing conditions, there was a potential that NMES would affect both conditions differentially. Therefore the effects of NMES on MEPs recorded during *both* pre-activation tasks were investigated.

The procedures used during the reflexive swallowing condition were not well tolerated by a number of participants. As the subsequent investigations involved recording a substantial number of trials, investigation of the reflexive swallowing condition was discontinued. This compromise was justified as swallowing-related MEPs were recorded during the pharyngeal phase of volitional swallowing, providing insight into the motor control of this reflexive phase. Further, the reflexive swallowing condition was limited by similar constraints as discussed in the context of the fMRI study undertaken by Kern et al. (2001a). While participants were unable to predict the exact time of the next water infusion, some voluntary activation of muscle fibres in anticipation of the impending bolus may have occurred. This may explain why MEPs were measurable in some participants during this muscle pre-activation condition, while they were absent in most other participants. However, the evaluation of truly naïve, reflexive swallowing is difficult as informed consent is an important prerequisite for inclusion in any research project. Further, reflexive swallowing occurs infrequently, thus making event-related assessment of biomechanical and neurophysiological measures a lengthy process. The evaluation of the reflexive, pharyngeal phase of swallowing thus offers a valuable alternative for investigating reflexive components of swallowing.

Since no previous studies in the area of swallowing research have evaluated MEPs recorded during muscle pre-activation, it was unknown whether task-related MEPs are a reliable measure of corticobulbar excitability in a functional context. Intraclass correlation analysis revealed moderate to high reliability for the data recorded within one and across multiple sessions. Similarly, inter- and intra-rater reliability was high. These findings are in agreement with previous research, which has indicated that MEPs recorded at rest are a reliable means for mapping the cortical motor representation of muscles involved in swallowing (Plowman-Prine et al., 2008).

Further indication that mean MEP measures are a reliable means of evaluating corticobulbar excitability can be derived from the reliability study undertaken to investigate the stability of MEP measures across time (Chapter 8). This investigation revealed no changes of mean MEP amplitude and onset latency across a 2 hr period. Trial-by-trial and inter-individual variability was reflected in large standard deviations, which is in agreement with prior reports of intrinsic fluctuations of cortical excitability across time (Wassermann, 2008). Averaging likely reduced the degree of intra-individual short-term variability. MEPs recorded during functional muscle pre-activation are, therefore, a reliable measure of corticobulbar excitability across a 2 hr timeframe. A further confound in the evaluation of event-related NMES was the possibility that repeated swallowing alone affects corticobulbar excitability. This was not found to be the case (Chapter 8). Together, these findings indicate that MEPs provide a reliable means of evaluating treatment effects induced by swallowing-related NMES across an extended period of time and investigation of various treatment protocols within the same individual across multiple sessions.

Across all investigations undertaken in the framework of this research programme, a total of 83 volunteers were screened for MEPs. Discernable MEPs were recorded in 57 of these participants (68.7%). A comparable ratio has been reported previously for the biceps brachii muscle, which was “primarily inexcitable by focal TMS of the contralateral motor cortex” in 4 of 11 research participants (36.4%) (Ziemann et al., 1998, p. 1116). Similarly, Macaluso et al. (1990) reported lower MEP amplitudes and higher motor thresholds for the masseter muscle compared to hand muscles. Either of the following three phenomena, or a combination of them, may explain these inter-individual differences: It is possible that (a) in some participants screened for inclusion into this research programme, the threshold for activating submental corticobulbar projections exceeded the level of stimulation provided by TMS. While pre-activation may have lowered this activation threshold, the evoked motor responses may have been too small to be clearly distinguishable from the task-related background sEMG activity. Macaluso et al. (1990) proposed that (b) differences in the nature of MEP recorded from masseter muscles and hand muscles may relate to a smaller number of crossed neural connections between the respective area of M1 and the masseter muscle in some participants. Consequently, any descending masseter motor volleys would be relatively smaller than those controlling the hand musculature. It is also possible that (c) existing connections were not optimally activated by the induced magnetic field. This may be related to an unfavourable angle between the orientation of the neurons of interest and the orientation of the magnetic field, as only those neurons oriented perpendicular to the magnetic field will be excited maximally. If all or the majority of these neurons lie in parallel with the magnetic field, the evoked response may be so small as to be undiscernible from the background sEMG recorded at the periphery during muscle contraction.

Therefore, inter-individual neuroanatomical differences likely account for the varying ability to record MEPs from the submental muscle group. It would be of interest to establish whether (a) other research groups evaluating MEPs as a measure of motor cortical excitability have observed a similar phenomenon in other muscle groups, whether (b) an approximate ratio of presence versus absence of MEPs can be determined, and whether (c) this ratio is dependent on the muscle under investigation and related to the size of its representation in the motor cortex.

For the event-related and non-event-related NMES investigations, the optimal location on the scalp for eliciting MEPs was determined during the voluntary muscle contraction task. TMS was administered over the same optimal scalp location during the volitional swallowing conditions. It may be argued that this methodological approach is the underlying cause for the differences in the amplitude and ability to record MEPs during the two muscle pre-activation conditions, if different areas of M1 are responsible for the motor control of the submental muscle group during different motor tasks. In participants who did not display MEPs during the swallowing condition, the area involved in the motor control of this task may be distinctly different from the area involved in the motor control of voluntary muscle contraction. In participants who displayed swallowing-related MEPs, albeit of smaller amplitude, these areas may be distinct, but overlapping. However, this hypothetical scenario is unlikely, because it implies functional motor cortical organisation rather than anatomical cortical organisation of the motor cortex. Indeed, previous research using fMRI has demonstrated that the lateral primary motor cortex was activated during both volitional tongue elevation and volitional swallowing tasks (Martin et al., 2004). Further, single-neuron studies of the primate tongue M1 have shown that neurons fire during both volitional tongue movements and swallowing (Martin, Murray, Kemppainen, Masuda & Sessle, 1997). Martin et al.

(2004) concluded “this evidence suggests that the lateral pericentral cortex mediates the execution of tongue movements produced within a variety of behavioural contexts” (p. 2438). The same is likely to be true for the submental musculature.

In summary, this research programme showed that MEPs recorded during functional muscle pre-activation are a reliable measure of corticobulbar excitability across a 2 hr timeframe and across multiple sessions. The employed methodologies allow investigation of the corticobulbar projections to the submental muscle group in the functional context of volitional contraction and the pharyngeal phase of volitional swallowing. The results documented in this research programme therefore provide reliable information about the effects of NMES on task-related corticobulbar excitability and new insights into our understanding of the motor control of swallowing.

14.2: Implications for the Neural Control of Swallowing

Aside from the identification of optimal stimulation parameters for NMES of the submental muscle group, a second important finding of this research programme was the observation of distinct differences in the MEPs recorded during volitional contraction and the swallowing conditions. Specifically, the amplitude of MEPs recorded during the VC condition were larger compared to those recorded during the VPS condition and the likelihood of recording discernable MEPs decreased along a continuum of increasing reflexive control of the performed motor tasks. Based on these findings, and the contradicting reports on the involvement of M1 in the motor control of the reflexive, pharyngeal phase of swallowing, two models of neural control networks are proposed to explain the results documented in the present

study. In general, these models are based on two different views about the involvement of M1 in the motor control of this phase of swallowing.

Firstly, differences in MEP facilitation may be related to differences in the degree of motor cortical activation during task performance (pyramidal cortical control model, Figure 22, p. 184). As the contraction task is purely voluntary, greater neural output to motor neuron pools in the brainstem results in greater pre-activation of the neural pathway and ultimately greater facilitation of MEP amplitude. During volitional swallowing, a smaller number of suprabulbar motor neurons may be recruited, consequently resulting in reduced facilitation of MEP amplitude. According to this model, the differences in MEP amplitude are therefore ultimately related to non-equal descending cortical motor output along the same cortico-peripheral pathway. In the participants who did not display MEPs during the VPS condition, corticobulbar facilitation may have been insufficient to evoke discernable motor responses that are greater than sEMG background activity. This model is based on the assumption that M1 is involved in the motor control of the pharyngeal phase of swallowing, which is supported by reports of primary motor cortex activation during volitional swallowing (Hamdy et al., 1999a; Martin et al., 2001; Kern et al., 2001a; Kern et al., 2001b; Martin et al., 2004; Toogood et al., 2005). In agreement with the hypothesis underlying the pyramidal cortical control model, some fMRI investigations reported less M1 activation during volitional swallowing compared to a volitional tongue elevation task (Martin et al., 2004). This finding, however, is contrasted by other reports that did not find differences (Kern et al., 2001b). In summary, the pyramidal cortical control model argues that M1 is involved in the motor control of pharyngeal phase swallowing and that the differences in MEP amplitudes recorded during VC and VPS are related to differences in the magnitude of the descending motor volleys.

In contrast, the second model (non-pyramidal cortical modulation model, Figure 23, p. 186) argues that M1 is not involved in the motor control of the pharyngeal phase of swallowing and that two distinctly different neural networks control the execution of the two tasks. According to this model, activation of the SMA directly excites the swallowing pattern generators located in the medulla of the brainstem, either by completely bypassing the M1 of the submental musculature or by activating it to a very minor degree. Lower amplitude of MEPs triggered by volitional swallowing relates to the relative inactivity of the submental M1, compared to that present for volitional contraction. This difference accounts for the lesser degree of MEP facilitation during volitional swallowing.

This model is in line with the generally accepted concept that the neural control of the swallowing reflex is orchestrated by central pattern generators in the brainstem (Jean, 2001). It is further supported by previous research employing EEG, which has documented a relative quiescence (Huckabee et al., 2003) or minor activation of M1 (Satow et al., 2003) during the pharyngeal phase of volitional swallowing. Prior reports that M1 is not involved in the motor control of reflexive motor tasks offer further support for this model (Regan, 1989).

The comparison of MEPs recorded during the different muscle contraction conditions provides evidence for differences in the magnitude of MEP facilitation during these tasks, but cannot clearly support one model in favour of the other. Future studies are needed to tease apart the relative contribution of the motor cortex to the motor control of the heavily intertwined oral and pharyngeal phases of swallowing. Some of the results documented in this research programme may be interpreted in the context of the two proposed models.

In particular, the findings that event-related NMES affected MEPs recorded during the VC, but not those recorded during the VPS condition, are noteworthy.

One would have expected swallowing-related MEPs to be affected by event-related NMES for two reasons: One, NMES stimulus trains were paired with the execution of volitional swallows, providing a close link between sensorimotor stimulation and functional context. Two, previous research has reported improved (Fraser et al., 2002) or declined swallowing function (Power et al., 2004), which was related to changes in MEPs recorded at rest. It would appear likely that MEPs recorded *during* swallowing would also be affected by NMES. In contrast, swallowing-related MEPs consistently remained unaffected in each of the investigations undertaken in this research programme.

Three questions emerge from these findings: (1) why were MEPs recorded during the pharyngeal phase of swallowing not affected by the apparent changes in M1 excitability, (2) if this implies that M1 is not involved in the pharyngeal phase of swallowing, why did event-related NMES induce changes in M1 excitability, and (3) why did Fraser et al. (2002) find a relationship between increased corticobulbar excitability and improved swallowing function?

Absent effects on MEPs recorded during VPS can be interpreted in support of the non-pyramidal cortical modulation model, which argues that M1 is not involved in the motor control of the pharyngeal phase of swallowing. MEPs recorded during this phase would consequently not be affected by changes in the excitability of neuronal pathways originating in this area. If this model is correct, the question arises why swallowing-related NMES affected the excitability of M1, as evidenced by altered MEP amplitudes recorded during VC, if M1 was not activated when event-related NMES was administered. The reasons for this are unclear. It may be argued that event-related NMES affects the primary motor area of the stimulated muscle, even when it is not directly activated during NMES. This hypothesis is supported by the results documented by Fraser et al. (2002) and Power

et al. (2004), who reported effects on MEPs in response to NMES administered when the stimulated muscle was at rest. This does not, however, explain why non-event-related NMES did not induce changes in M1 excitability in our study; clearly, our results favour administration of NMES in a functional context. The instructions given to the research participants for the event-related NMES treatment may provide another possible explanation. Participants swallowed as they normally would, without limiting oral movements. This is in contrast to the swallows performed during MEP acquisition, where participants limited oral movements and directly initiated a pharyngeal swallow. During event-related NMES treatment trials, this task therefore included a volitional motor component, which is subject to M1 motor control.

The question of why Fraser et al. (2002) observed functional changes in response to non-event-related NMES relates to this hypothesis. As discussed in Chapter 10, it is possible that increased or decreased corticobulbar excitability primarily affected the motor control of volitional oral movements, in particular of the tongue and BOT. Improved or impaired BOT drop may affect the timely onset of pharyngeal swallowing and thus explain the functional effects reported by Fraser et al. (2002) and Power et al. (2004).

If the above hypotheses in explanation of the three questions are the underlying causes for the observed phenomena, two important conclusions can be drawn from these findings. One, the primary motor area is not involved in the motor control of the pharyngeal phase of volitional swallowing (as proposed by the non-pyramidal cortical modulation model). Two, event-related NMES triggered by volitional swallowing has the potential to increase the excitability of corticobulbar motor projections to the submental muscle group during volitional contraction, but may not during volitional swallowing. Regardless, increased excitability of

corticobulbar projections might be linked to improvements of swallowing function, as suggested by prior research (Fraser et al., 2002). However, this relationship remains to be investigated for the submental muscle group.

Further support for the non-pyramidal cortical modulation model can be derived from previous research, which has documented that MEPs recorded during a series of complex finger movement tasks were larger than those recorded during simple finger abduction (Flament et al., 1993). One could argue that swallowing represents a more complex motor task than submental muscle contraction. If M1 was directly involved in the motor control of both tasks, it would be expected that MEPs recorded during the VPS condition are larger than those recorded during the VC condition. This was not found to be the case.

If M1 is indeed not directly involved in the motor control of the pharyngeal phase of swallowing, then another question arises from this observation: is the evaluation of task-related MEPs a valid approach for establishing treatment effects on motor cortical excitability during pharyngeal swallowing? Changes in corticobulbar excitability, reflected in varying MEP amplitude during volitional contraction, were not detectable in MEPs recorded during pharyngeal swallowing. Therefore, evaluation of MEPs may be more suitable for investigating changes in cortical excitability during volitional movements, such as those required during the oral preparatory and transit phases, rather than the reflexive pharyngeal phase.

14.3: NMES treatment parameters and the role of NMES in swallowing rehabilitation

The primary objective of this research programme was to identify optimal stimulation parameters for NMES administered to the submental muscle group. This research is imperative because of contradictory reports about the efficacy of NMES

in swallowing rehabilitation and a lack of research identifying the effects of this treatment modality on neurophysiological measures of swallowing. In a series of projects, the effects of the parameters of NMES frequency and dose on MEP amplitude and onset latency were evaluated, and differences between event-related and non-event-related NMES investigated. Outcome measures were recorded in the functional context of muscle contraction. Excitatory effects were documented after 60 repetitions of swallowing-triggered stimulus trains of 4 s duration, with a stimulus frequency of 80 Hz. In contrast, 5 Hz and 20 Hz NMES were found to induce inhibition of the excitability of corticobulbar projections to the submental muscle group. Maximal effects were observed at 60 min post treatment in response to both excitatory and inhibitory NMES treatment trials. Compared to non-event-related NMES, event-related NMES produced superior results in increasing corticobulbar excitability, even when non-event-related NMES was administered for 1 hr continuously.

The frequency-specificity of the induced effects and the time course over which these effects evolved post treatment is in agreement with the findings of research employing similar methodologies (Fraser et al., 2002; Power et al., 2004). The documented patterns lend support to the hypothesis that LTP and LTD are responsible for the observed effects. Specifically, LTP occurs as a result of coincident excitation of pre- and post-synaptic elements (Bliss & Gardner-Mewin, 1973). In this study, high frequency stimulation of the fast-twitch fibres of the submental muscle group occurred simultaneously with endogenous activation of these fibres during swallowing. In contrast, low frequency stimulation likely induced a mismatch of pre- and post-synaptic activation, which has been shown to induce processes of LTD (Dudek & Bear, 1992; Markram et al., 1997). In addition, the time course of 60 min over which the effects evolved has previously been linked to

processes underlying LTP or LTD induction (Malenka & Nicoll, 1999; Thompson et al., 1999). This time course has been related to depolarisation of the post-synaptic cell in response to repetitive synaptic activation, which releases Mg^{2+} ions from blocking N-methyl-D-aspartate (NMDA) receptor gated ion-channels in the cell membrane. This consequently allows the rapid influx of Ca^{2+} ions into the post-synaptic cell, a process thought to increase synaptic strength for up to 2 hrs (Malenka & Nicoll, 1999; Thompson et al., 1999).

The finding that non-event related NMES did not affect corticobulbar excitability provides further support for the hypothesis that LTP and LTD mechanisms underlie these effects. This is in line with the hypothetical concept that peripheral sensorimotor stimulation administered in a functional context is more effective. Indeed, when event-related and non-event-related NMES were administered at the same stimulation parameters, changes in corticobulbar excitability only occurred after event-related NMES. Even when non-event-related NMES was administered at a high dose for 1 hr, no changes in corticobulbar excitability were observed. These results are corroborated by clinical reports that documented no effects of non-event-related NMES on functional measures of the upper extremities (DeKroon et al., 2005, Holcomb et al., 2006) and support the view that concomitant exogenous and endogenous neural activation facilitate induction of lasting effects in the central nervous system.

The effects induced by event-related NMES may be linked to an underlying down-regulation of cortical inhibitory neurons during voluntary contraction. The influence of voluntary contraction on intracortical inhibition networks has been assessed with paired-pulse TMS, which induces short-term intracortical inhibition (SICI), when a sub-threshold conditioning stimulus is delivered prior to a super-threshold test stimulus at an interval of 1-5 ms (Ridding, Taylor & Rothwell, 1995).

During voluntary muscle activation, SICI was found to be reduced, reflecting a decrease in the net excitability of inhibitory neuronal networks, which are mediated by gamma-aminobutyric acid (GABA) receptors. It is therefore plausible that during event-related NMES, net cortical excitability is greater than during non-event-related NMES at rest, enhancing the potential for induction of neural plasticity by peripheral sensorimotor stimulation. The beneficial influence of down-regulating cortical inhibitory networks is further reflected by the fact that in *in vitro* animal research, GABAergic antagonists are often used to facilitate the induction of LTP (Bindman, Murphy & Pockett, 1988).

The observed findings are in contrast to those reported by Fraser et al. (2002) and Power et al. (2004), who documented changes in MEP amplitude, and functional measures of swallowing, in response to non-event-related NMES of the pharyngeal and faucial pillar musculature, respectively. Why this type of NMES resulted in changes in corticobulbar excitability in their studies, and not in the present investigations, is unclear. Similarly, non-event-related NMES of the quadriceps femoris muscle resulted in increased muscle strength compared to no exercise (Bax et al., 2005). It may be that the dose of non-event-related NMES administered in our investigations was either insufficient or too large to induce central effects. This hypothesis is based on reports of an optimal window of stimulation duration, reported by Fraser et al. (2002). In their study, MEP amplitude increased after 10 min of NMES, whereas stimulation for 5 min or 20 min did not affect corticobulbar excitability. It is possible that changes could have occurred in response to non-event-related NMES in the present investigations, had a different dose been administered. This dose would likely represent a level between the low and high doses evaluated here. Further investigation into this hypothesis is warranted.

An alternative explanation for the discrepant results relates to the stimulation parameters employed during non-event-related NMES in our investigations, which were based on the optimal parameters identified for event-related NMES. It is possible that these parameters are not optimal for non-event-related NMES and that effects could have occurred, had different stimulation parameters been employed. Indeed, Fraser et al. (2002) and Power et al. (2004) identified much lower NMES frequencies to be optimal for inducing cortical effects after non-event-related NMES of other corticobulbar muscles. This phenomenon warrants further investigation.

Evaluation of the optimal dose of event-related NMES revealed that only the largest number of the tested stimulus train repetitions induced excitatory effects. It is possible that a greater number of repetitions would produce even greater effects. Previous research has reported increases in corticobulbar excitability of approximately 175% of pre-treatment baseline (Fraser et al., 2002), whereas in the present investigations, maximal changes reached approximately 127% of pre-treatment baseline. In this context, however, it is important to consider the optimal window of stimulation duration, documented to lie between 5 min and 20 min for non-event-related NMES (Fraser et al., 2002). Based on this observation, it is possible that above a certain threshold, the increase in the magnitude of the induced effects plateaus, and further increases in sensorimotor input have no, or possibly inhibitory, effects. This may also be true for event-related NMES. The underlying reason for such a phenomenon may relate to the synchronous nature of NMES, which is metabolically highly demanding, potentially inducing neuronal or muscular fatigue, or both (see Chapter 3 for review). Thus, more precise definition of the optimal window of benefit may further optimise the treatment effects documented here.

The large number of repetitions required to induce beneficial effects may, however, limit the applicability of swallowing-related NMES in clinical dysphagia rehabilitation, where many patients struggle to initiate swallowing. Swallowing-triggered NMES may therefore be limited to those patients who have retained a suitable level of functional ability. It would be of interest to investigate whether increases in corticobulbar excitability could also be induced by event-related NMES that is triggered by volitional contraction of the submental muscle group. If this is the case and potential excitatory effects are linked to improved swallowing function, then this treatment approach may provide an alternative for individuals with impaired swallowing biomechanics. As muscles would be stimulated outside the context of a functional swallow, this treatment approach would primarily target overall contractile strength. This may ultimately lead to increased hyo-laryngeal elevation and thus be indicated for patients with poor hyo-laryngeal elevation. Whether such a treatment produces superior results to the commonly used headlift exercise (Shaker et al., 1997), which is designed to increase submental muscle strength, remains to be established. If effective, it may provide a feasible alternative to the headlift exercise, the performance of which may be difficult for elderly or fragile individuals.

Comparison of the findings documented in this research programme with results reported by previous research is difficult, as the methodologies employed in most clinical research vary substantially from the research paradigm employed here. However, the results of some studies lend support to the findings of this research programme. For example, Burnett et al. (2005) demonstrated that self-triggered electrical stimulation of unilateral mylo- and thyro-hyoid muscles did not significantly affect the amplitude and duration of EMG activity recorded from either muscle during volitional swallowing. The authors suggested "...the central pattern

generator for hyo-laryngeal elevation is immutable with short term stimulation that augments laryngeal elevation during the reflexive, pharyngeal phase of swallowing” (Burnett et al., 2005, p. 4011). This finding is in line with the observation presented here that event-related NMES did not have immediate effects on the excitability of corticobulbar projections to the submental musculature during swallowing.

Similarly, Suiter et al. (2006) documented that sEMG activity recorded from the thyrohyoid musculature during swallowing did not change after two weeks of VitalStim™ intervention, a treatment approach, which also uses 80 Hz NMES.

However, neither of these studies evaluated the effects of NMES on EMG or sEMG measures related to volitional muscle contraction. Based on the findings of increased MEP amplitude during volitional contraction, changes in muscle activity may be present for this condition.

Power et al. (2006) evaluated the effects of non-event-related NMES of the faucial pillars on swallowing function in patients presenting with delayed onset of swallow. Although optimal stimulation parameters were used (Power et al., 2004), no improvements in swallowing function were documented. This finding is surprising, given the previously established relationships between swallowing function and pharyngeal or faucial pillar corticobulbar excitability in healthy individuals (Fraser et al., 2002; Power et al., 2004). The authors hypothesised that the magnitude of changes in the excitability of projections to the faucial pillars may have been insufficient to induce improvements in swallowing function or that confounding factors, such as lingual impairments, may be the underlying cause for this finding. This study underscores the importance of establishing links between the excitability of corticobulbar projections to the submental muscle group and swallowing function, not only in healthy participants, but patients presenting with a number of clinical subtypes of dysphagia. Clinically, the choice of treatment has to

be based on the specific pathophysiology of each patient, and any given treatment cannot address all pathophysiological impairments. For the patients enrolled in the study by Power et al. (2006), the administered form of NMES may not have addressed the underlying pathology that caused the swallowing impairments in this patient group.

In summary, the results established by this research programme provide important information about the differential effects of various NMES parameters on the degree of corticobulbar excitability during volitional contraction and pharyngeal phase swallowing. It has been shown that swallowing-triggered NMES has the potential to induce excitatory and inhibitory central effects and that these are depended on the frequency, dose and task context of the stimulation. A relationship of these changes to swallowing function remains to be established.

14.4: Limitations, Relevance and Future Directions

The findings of this research programme are subject to a number of limitations. Only a subset of the many possible combinations of NMES parameters was evaluated. Parameters were chosen based on previous research paradigms and treatment protocols, and were limited to six parameters evaluated in the event-related NMES investigations or three parameters evaluated in the non-event-related NMES investigations. The optimal treatment parameters identified for event-related NMES were employed in the non-event-related NMES protocols. It may be argued that different functional contexts warrant different optimal stimulation parameters. Further research is indicated to investigate this issue.

Due to the relatively large standard deviations, resulting from inter-individual differences in MEP amplitude and varying magnitude of change in response to NMES, statistical power of some comparisons is non-optimal. This

limits the interpretation of some of these data and warrants replication in a larger participant cohort.

As discussed above, the methodologies employed during the reflexive swallowing condition are limited by similar constraints as those discussed in the context of the fMRI studies by Kern et al. (2001a) and Martin et al. (2001). These limitations are closely related to the nature of informed research and temporal constraints.

This research programme has only evaluated the effects of NMES on measures of *motor* control related to volitional contraction and pharyngeal phase swallowing. Changes in *sensory* function related to these tasks have not been investigated. Due to the closely linked integration of motor and sensory components of swallowing, it is possible that changes in central sensorimotor integration networks occurred in response to NMES. Whether or not such changes occurred and, importantly, how they relate to swallowing function remains to be investigated.

Despite these limitations, this research programme provided important information about the effects of NMES on measures of swallowing neurophysiology. It established optimal stimulation parameters for NMES administered to the submental muscle group, which has central clinical relevance. It further developed and tested a method of evaluating corticobulbar excitability in a task-related context. Additionally, it contributed important new information to our understanding of neural networks governing the motor control of the pharyngeal phase of swallowing by offering two models of swallowing neural networks. While these models require further testing, some of the results documented by this research programme contribute to the interpretation and evaluation of these models.

As discussed throughout this thesis, there is a substantial need to further investigate the effects of NMES on neurophysiological, biomechanical and sensory

measures related to swallowing. This research may be undertaken in healthy research participants initially, but will ultimately need to be expanded to include patient groups presenting with various subtypes of dysphagia. An important next step will be to establish whether the documented increase in the amplitude of MEPs recorded during volitional contraction relates to improved swallowing function. Functional outcome measures may include the magnitude of submental sEMG activity, videofluorographic evaluation of pharyngeal biomechanics, such as the degree of hyo-laryngeal elevation and UOS opening, and pharyngeal sensory testing employing Functional Endoscopic Evaluation of Swallowing with Sensory Testing (FEESST). It is noteworthy that few techniques are available in swallowing research to precisely determine the integrity of oral and pharyngeal sensory networks. Before the precise effects of NMES on sensory function in swallowing can be established, it may be necessary to advance the currently available sensory testing tools.

Beside functional improvements, the increased corticobulbar excitability induced by event-related NMES may also facilitate neural plasticity, that is, motor learning in response to therapeutic intervention. It will therefore need to be established whether event-related NMES administered before a “traditional” dysphagia treatment session increases the effectiveness of the latter. Such benefits have been demonstrated for the first dorsal interosseus muscle, where peripheral NMES facilitated subsequent training of a complex motor task, accompanied by a strong trend for functional improvements to be greater than in a non-stimulated control group (McDonnell & Ridding, 2006). Similarly, stroke patients who received peripheral stimulation prior to a motor training session displayed greater improvements in a grip-lift task than a patient control group, which received sham stimulation (McDonnell, Hillier, Miles, Thompson & Ridding, 2007). Ziemann, Corwell and Cohen (1998) demonstrated that altered peripheral sensory input by

ischemic nerve block of the forearm increased the modifiability of motor cortical excitability in response to low intensity repetitive TMS, which on its own does not induce changes in cortical excitability.

It will be of further interest to establish whether event-related NMES triggered by volitional contraction induces changes in corticobulbar excitability, and whether these changes are related to improved or decreased swallowing function, as determined by the abovementioned outcome measures.

There is an additional need to investigate the neural networks underlying unimpaired swallowing. Thorough understanding of swallowing neurophysiology, and its correlation to biomechanical function, will enable a better evaluation, and ultimately more precisely targeted treatment of swallowing disorders. For this, isolated evaluation of volitional and reflexive components of swallowing may provide important new information. New approaches of separating the heavily intertwined phases of swallowing may facilitate this research. Additional research is specifically required into the precise role of peripheral sensory input to the swallowing motor plan, and how altered sensory input affects motor behaviour. New, functional brain imaging techniques with high temporal and spatial resolution will be of great value for these investigations.

Chapter 15: Concluding Remarks

This research programme established the effects of NMES on the excitability of corticobulbar projections to the submental muscle group. The results documented here suggest that 60 repetitions of swallowing-triggered NMES stimulus trains of 4 s duration, with a stimulus frequency of 80 Hz, induce an increase in corticobulbar excitability. Facilitation was only observed during a voluntary muscle pre-activation condition, and not during the pharyngeal phase of swallowing, suggesting that NMES affects voluntary, but not reflexive, components of the swallowing motor sequence. Non-event-related NMES did not affect corticobulbar excitability underlying either muscle pre-activation condition, suggesting that administration of NMES in a functional context is imperative for inducing lasting changes in corticobulbar excitability.

These findings provide answers to the key research questions laid out in the introduction chapter of this thesis. In particular, optimal stimulation parameters have been identified for event-related NMES of the submental musculature, which is of important clinical relevance. However, before event-related NMES can be applied in the clinical dysphagia rehabilitation setting, identification of functional benefits during swallowing in response to the documented increase in corticobulbar excitability is warranted. Until functional benefits are documented, and patient groups who benefit most from this intervention are identified, event-related NMES cannot be justified as a routine clinical application for swallowing rehabilitation. That said, careful, closely monitored experimental application of this treatment approach will provide urgently needed clinical information about the effects of NMES on impaired swallowing function.

The results of this research programme further provide important new insights into neural networks underlying volitional and reflexive components of swallowing function. Differences in the amplitude and occurrence of MEPs recorded during volitional and reflexive components of swallowing suggest that differences exist in the underlying neural networks governing the motor control the performed tasks. In particular, the magnitude of activation of the primary motor area may differ during volitional and reflexive contraction of the submental muscle group. This observation has important implications for the application of volitionally initiated, or passively administered, neurorehabilitative exercises. For NMES, the findings of this research programme indicate that stimulation administered in a functional context provides superior results compared to non-event-related NMES.

The methodology designed for this research programme was documented to provide reliable measurement of corticobulbar excitability in a functional context. Therefore, future investigations may employ TMS, triggered from contraction-related sEMG, to investigate corticobulbar excitability in a functional context.

In summary, this research programme successfully answered key scientific questions about the effects of NMES on neurophysiological measures of swallowing. It further provided new information about neural networks governing the motor control of pharyngeal phase swallowing. New directions for basic and clinical research were derived from these findings, which will eventually lead to a more precise definition of the role of NMES in swallowing rehabilitation.

References

- Abe, S., Wantanabe, Y., Shintani, M., Tazaki, M., Takahashi, M., Yamane, G.Y. et al. (2003). Magnetoencephalographic study of the starting point of voluntary swallowing. *Cranio*, 21(1), 46-49.
- Agur, A. M. R., & Lee, M. J. (1999). *Grant's Atlas of Anatomy*. Philadelphia, PA: Williams & Wilkins.
- Aine, C. J. (1995). A conceptual overview and critique of functional neuroimaging techniques in humans: I. MRI/fMRI and PET. *Critical Reviews in Neurobiology*, 9, 229-309.
- Amassian, V. E., Stewart, M., Quirk, G. J., & Rosenthal, J. L. (1987). Physiological basis of motor effects of a transient stimulus to cerebral cortex. *Neurosurgery*, 20, 74-93.
- American Physical Therapy Association. (1990). *Electrotherapeutic Terminology in Physical Therapy. Section on Clinical Electrophysiology*. Alexandria, VA: Author.
- American Psychological Association. (2001). *Publication Manual of the American Psychological Association* (5th ed.). Washington, DC: Author.
- Asanuma, H., & Keller, A. (1991). Neurobiological basis of motor learning and memory. *Concepts in Neuroscience*, 2, 1-30.
- Atkinson, G., & Nevill, A. M. (1998). A review of the statistical methods employed to assess measurement error (reliability) in variables relevant in sports medicine. *Sports Medicine*, 26, 217-38.
- Baijens, L. W. J., Speyer, R., Roodenburg, N., & Manni, J. J. (2008). The effects of neuromuscular electrical stimulation for dysphagia in opercular syndrome: a case study. *European Archives of Otorhinolaryngology*, 265, 825-830.
- Baker, L. L., McNeal, D. R., Benton, L. A., Bowman, B. R., & Waters, R. L. (1993). *NeuroMuscular Electrical Stimulation: A Practical Guide* (3rd ed.). Downey, CA: Los Amigos Research and Education Institute, Inc.

- Basmajian, J. V., & DeLuca, C. (1985). *Muscles alive: their functions revealed by electromyography*. C. Deluca (Ed.) Baltimore, MA: Lippincott, Williams&Wilkins.
- Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive stimulation of human motor cortex. *Lancet* *1*, 1106-1107.
- Barker, A.T. (1999). The history and basic principles of magnetic nerve stimulation. *Electroencephalography Clinical Neurophysiology Supplement*, *51*, 3-21.
- Bartholow, R. (1874). Experimental investigations into the function of the human brain. *American Journal of the Medical Sciences*, *134*, 305-313.
- Bax, L., Staes, F., & Verhagen A. (2005). Does neuromuscular electrical stimulation strengthen the quadriceps femoris? *Sports Medicine*, *35*, 191-212.
- Bear, M. F., Connors, B.W., & Paradiso, M.A. (2006). *Neuroscience: Exploring the Brain* (3rd ed.). Baltimore, MD, Lippincott Williams&Wilkins.
- Benecke, R., Meyer, B. U., Schoenle, P., & Conrad, B. (1988). Transcranial magnetic stimulation of the human brain: responses in muscles supplied by cranial nerves. *Experimental Brain Research*, *71*, 623-632.
- Bestmann, S. (2007). The physiological basis of transcranial magnetic stimulation. *Trends in Cognitive Sciences* *12*(3), 81-83.
- Bindman, L. J., Murphy, K. P. S. J., & Pockett, S. (1988). Postsynaptic control of the induction of long-term changes in efficacy of transmission at neocortical synapses in slices of rat brain. *Journal of Neurophysiology*, *60*, 1053-1065.
- Bliss, T. V. & Lomo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anesthetized rabbit following stimulation of the perforant path. *Journal of Physiology*, *232*, 331-356.
- Bliss, T. V. P., & Gardner-Mewin, A. R. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the unanaesthetized rabbit following stimulation of the perforant path. *Journal of Physiology*, *232*, 357-374.

- Blumenfeld, L., Hahn, Y., LePage, A., Leonard, R., & Belafsky, P. C. (2006). Transcutaneous electrical stimulation versus traditional dysphagia therapy: a nonconcurrent cohort study. *Otolaryngology, Head and Neck Surgery*, *135*, 754-757.
- Bolton, D. A. E., Cauraugh, J. H., & Hausenblas, H. A. (2004). Electromyogram-triggered neuromuscular stimulation and stroke motor recovery of arm/hand functions: a meta-analysis. *Journal of Neurological Sciences*, *223*, 121-127.
- Boyd, S. G., Rothwell, J. C., Cowan, J. M. A., Webb, P. J., Morley, T., Asselman, P. et al. (1986). A method of monitoring function in cortical pathways during scoliosis surgery with a note on motor conduction velocities. *Journal of Neurology Neurosurgery Psychiatry*, *49*, 251-257.
- Brandt, S. A., Ploner, C. J., & Meyer, B. U. (1997). Repetitive transkranielle Magnetstimulation. *Der Nervenarzt*, *68*, 778-784.
- Brasil-Neto, J. P., Cohen, L. G., Panizza, M., Nillsen, J., Roth, B. J. & Hallett, M. (1992). Optimal focal transcranial magnetic activation of the human motor cortex, effect of coil orientation, shape of the induced current pulse, and stimulus intensity. *Journal of Clinical Neurophysiology*, *9*, 132-136.
- Bueteifisch, C. M., Davis, B. C., Wise, S. P., Sawaki, L., Kopylev, L., Classen J. et al. (2000). Mechanisms of use-dependent plasticity in the human motor cortex. *Proceedings of the National Academy of Sciences (USA)*, *97*, 3661-3665.
- Bueteifisch, C. M., & Cohen, L. G. (2008). Use-dependent changes in TMS measures. In E. M. Wassermann, C. M. Epstein, U. Ziemann, V. Walsh, T. Paus & S. H. Lisanby (Eds). *The Oxford Handbook of Transcranial Stimulation*. New York: Oxford University Press.
- Buelow, M., Speyer, R., Baijens, L., Woisard, V., & Ekberg, O. (2008). Neuromuscular electrical stimulation (NMES) in stroke patients with oral and pharyngeal dysfunction. *Dysphagia*, *23*(3), 302-309.
- Burnett, T. A., Mann, E. A., Cornell, S. A., & Ludlow, C. L. (2003). Laryngeal elevation achieved by neuromuscular stimulation at rest. *Journal of Applied Physiology*, *94*, 128-134.

- Burnett, T. A., Mann, E. A., Stoklosa, J. B., & Ludlow, C. L. (2005). Self-triggered electrical stimulation during swallowing. *Journal of Neurophysiology*, *94*, 4011-4018.
- Cacchio, A., Cimini, N., Alosi, P., Santilli, V., & Marrelli, A. (2009). Reliability of transcranial magnetic stimulation-related measurements of tibialis anterior muscle in healthy subjects. *Clinical Neurophysiology*, *120*, 414-419.
- Car, A. (1970). Cortical control of the bulbar swallowing center. *Journal of Physiology (Paris)*, *62*(4), 361-386.
- Carroll, T. J., Riek, S., & Carson, R. G. (2001). Reliability of the input-output properties of the cortico-spinal pathway obtained from transcranial magnetic and electrical stimulation. *Journal of Neuroscience Methods*, *112*, 193-202.
- Carnaby-Mann, G. D., Crary, M. A. (2008). Adjunctive neuromuscular electrical stimulation for treatment-refractory dysphagia. *Annals of Otology, Rhinology & Laryngology*, *117*, 279-287.
- Carnaby-Mann, G. D., Crary, M. A. (2007). Examining the evidence on neuromuscular electrical stimulation for swallowing. *Archives of Otolaryngology Head and Neck Surgery*, *133*, 564-571.
- Christie, A., Fling, B., Crews, R. T., Mulwitz, L. A., Kamen, G. (2007). Reliability of motor-evoked potentials in the ADM muscle of older adults. *Journal of Neuroscience Methods*, *164*, 320-324.
- Cooke, S. F., & Bliss, T. V. (2006). Plasticity in the human central nervous system. *Brain*, *129*, 1659-1673.
- Crary, M.A., Carnaby (Mann), G.D., Groher, M.E., & Helseth, E. (2004). Functional benefits of dysphagia therapy using adjunctive sEMG biofeedback. *Dysphagia*, *19*, 160-164.
- Cruccu, G., Berardelli, A., Inghilleri, M., & Manfredi, M. (1990). Functional organization of the trigeminal motor system in man. *Brain*, *112*, 1333-1350.
- Cunnington, R., Bradshaw, J. L., & Iansek, R. (1996). The role of the supplementary motor area in the control of voluntary movement. *Human Movement Science*, *15*, 627-647.

- Daniels, S. K., & Foundas, A. L. (1997). The role of the insular cortex in dysphagia. *Dysphagia*, 12(3), 146-156.
- Daniels, S.K. & Huckabee, M.L. (2008). *Dysphagia In Stroke*. San Diego, CA: Plural Publishing.
- Datta, A. K., Harrison, L. M., & Stephens, J. A. (1989). Task-dependent changes in the size of responses to magnetic brain stimulation in human first dorsal interosseous muscle. *Journal of Physiology*, 418, 13-23.
- Davey, K. (2008) Magnetic field stimulation: the brain as a conductor. In E. M. Wassermann, C. M. Epstein, U. Ziemann, V. Walsh, T. Paus & S. H. Lisanby (Eds). *The Oxford Handbook of Transcranial Stimulation*. New York: Oxford University Press.
- Day, B. L., Rothwell, J. C., Thompson, P. D., Dick, J. P. R., Cowan, J. M. A., Berardelli, A., et al. (1987). Motor cortex stimulation in intact man II: multiple descending volleys. *Brain*, 110, 1191-1209.
- Deecke, L., & Kornhuber, H. H. (1978). An electrical signal of participation of the mesial supplementary motor cortex in human voluntary finger movement. *Brain Research*, 159, 473-476.
- DeKroon, J. R., Ijzermann, M. J., Chae, J., Lankhorst, G.J., & Zilvold, G. (2005). Relation between stimulation characteristics and clinical outcome in studies using electrical stimulation to improve motor control of the upper extremity in stroke. *Journal of Rehabilitation Medicine*, 37, 65-74.
- Department of Health and Human Services, Food and Drug Administration. (1999). Guidance for Industry, FDA Reviewers/Staff and Compliance - Guidance Document for Powered Muscle Stimulator 510(k). Rockville, MD: Author.
- Department of Health and Human Services, Food and Drug Administration. (2001). Approval of VitalStim device (p. 103), retrieved on 23.03.2009 from <http://www.fda.gov/cdrh/pdf/K002410.pdf>
- Devanne, H., Lavoie, B. A., & Capaday, C. (1997). Input-output properties and gain changes in the human corticospinal pathway. *Experimental Brain Research*, 114, 329-338.

- Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995). Contributions of anterior cingulate to behaviour. *Brain*, *118*, 279-306.
- Diamant, N. E. (1989). Physiology of esophageal motor function. *Gastroenterological Clinics of North America*, *18*(2), 179-194.
- Doeltgen, S. H., Ridding, M. C., O'Beirne, G. A., Dalrymple-Alford, J., & Huckabee, M. L. (2009). Test-retest reliability of motor evoked potentials (MEPs) at the submental muscle group during volitional swallowing. *Journal of Neuroscience Methods*, *178*, 134-137.
- Doeltgen, S. H., Witte, U., Gumbley, F., & Huckabee, M. L. (2009). Evaluation of manometric measures during tongue-hold swallows. *American Journal of Speech and Language Therapy*, *18*, 65-73.
- Doty, R. W., & Bosma, J. F. (1956). An electromyographic analysis of reflex deglutition. *Journal of Neurophysiology*, *19*, 44-60.
- Dubner, R., Sessle, B. J., & Storey, A. T. (1978). *The neural basis of oral and facial function*. New York: Plenum.
- Dudek, S. M., & Bear, M. F. (1992). Homosynaptic long-term depression and effects of N-methyl-D-aspartate receptor blockade. *Proceedings of the National Academy of Science (USA)*, *89*, 4363-4367.
- Dziewas, R., Soeroes P., Ishii, R., Chau, W., Henningsen, H., Ringelstein, E. B. et al. (2003). Neuroimaging evidence for cortical involvement in the preparation and in the act of swallowing. *Neuroimage*, *20*, 135-144.
- Ebmeier, K. P., & Lappin, J. M. (2001). Electromagnetic stimulation in psychiatry. *Advances in Psychological Treatment*, *7*, 181-188.
- Edwards, H. E., Huang, Y. Z., Wood, N. W., Rothwell, J. C., & Bhatia, K. P. (2003). Different patterns of electrophysiological deficits in manifesting and non-manifesting carriers of the DYT1 gene mutation. *Brain*, *126*, 2074-2080.
- Ertekin, C., & Aydogdu, I. (2003). Neurophysiology of swallowing. *Clinical Neurophysiology*, *114*, 2226-2244.

- Fillipi, M. M., Oliveri, M., Vernieri, F., Pasqualetti, P., & Rossini, P. M. (2000). Are automatic signals influencing cortico-spinal motor excitability? A study with transcranial magnetic stimulation. *Brain Research*, 881, 159-164.
- Ferbert, A., Priori, A., Rothwell, J. C., Day, B. L., Colebatch, J. G., & Marsden, C. D. (1992). Interhemispheric inhibition of the human motor cortex. *Journal of Physiology*, 453, 525-546.
- Ferrier, D. (1873). Experimental researches in cerebral physiology and pathology. *West Riding Lunatic Asylum Medical Reports*, 3, 1-50.
- Flament, D., Goldsmith, P., Buckley, C. J., & Lemon, R. N. (1993). Task dependence of responses in first dorsal interosseous muscle to magnetic brain stimulation in man. *Journal of Physiology*, 464, 361-378.
- Fraser, C., Power, M., Hamdy, S., Rothwell, J., Hobday, D., Hollander, I. et al. (2002). Driving plasticity in the human adult motor cortex is associated with improved motor function after brain injury. *Neuron*, 34, 831-840.
- Fraser, C., Rothwell, J., Power, M., Hobson, A., Thompson, D., & Hamdy, S. (2003). Differential changes in human pharyngoesophageal motor excitability induced by swallowing, pharyngeal stimulation and anesthesia. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, 285, 137-144.
- Freed, M. L., Freed, L., Chatburn, R. L., & Christian, M. (2001). Electrical stimulation for swallowing disorders caused by stroke. *Respiratory Care*, 46, 466-474.
- Fritsch, G., & Hitzig, E. (1870). Ueber die elektrische Erregbarkeit des Grosshirns. Translation by G. von Bonin. In: *The cerebral cortex* (pp. 73-96). Springfield, IL: Thomas.
- Gallas, S., Moirrot, P., Debono, G., Navarre, I., Denis, P., Marie, J. P. et al. (2007). Mylohyoid motor-evoked potentials relate to swallowing function after chronic stroke dysphagia. *Neurogastroenterology and Motility*, 19, 453-458.
- Glanz, M., Klawansky, S., Stason, W., Berkey, C., & Chalmers, T.C. (1996). Functional electrostimulation on poststroke rehabilitation: a meta-analysis of the randomized controlled trials. *Archives of Physical Medicine and Rehabilitation*, 77, 549-553.

- Glinsky, J., Harvey, L., & VanEs, P. (2007). Efficacy of electrical stimulation to increase muscle strength in people with neurological conditions: a systematic review. *Physiotherapy Research International*, 12(3), 175-194.
- Golaszewski, S., Kremser, C. H., Wagner, M., Felber, S, Aichner F., & Dimitrijevic, M. M. (1999). Functional magnetic resonance imaging of the human motor cortex before and after whole-hand afferent electrical stimulation. *Scandinavian Journal of Rehabilitation Medicine*, 31, 165-173.
- Gow, D., Hobson, A. R., Furlong, P., & Hamdy, S. (2004). Characterising the central mechanisms of sensory modulation in human swallowing motor cortex. *Clinical Neurophysiology*, 115, 2382-2390.
- Guyton, A. C. (1986). *Textbook of Medical Physiology*. Philadelphia, PA: Saunders.
- Hallett, M. (2000). Transcranial magnetic stimulation and the human brain. *Nature*, 406, 147-150.
- Hamdy, S., Aziz, Q., Singh, K. D., Barlow, J., Hughes, D. G., Tallis, R. C., et al. (1996). The cortical topography of human swallowing musculature in health and disease. *Nature Medicine*, 2, 1217-1224.
- Hamdy, S., Aziz, Q., Rothwell, J. C., Hobson, A., Barlow, J., & Thompson, D. G. (1997). Cranial nerve modulation of human cortical swallowing motor pathways. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, 35, G802-G808.
- Hamdy, S., Aziz, Q., Rothwell, J. C., Hobson, A., & Thompson, D. G. (1998a). Sensorimotor modulation of human cortical swallowing pathways. *Journal of Physiology*, 506, 857-866.
- Hamdy, S., Aziz, Q., Rothwell, J. C., Power, M., Singh, K. D., & Nicholson, D. A. (1998b). Recovery of swallowing after dysphagic stroke relates to functional reorganization in the intact motor cortex. *Gastroenterology*, 115, 1104-1112.
- Hamdy, S., Mikulis, D. J., Crawley, A., Xue, S., Lau, H., Henry, S. et al. (1999a). Cortical activation during human volitional swallowing: an event-related fMRI study. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, 40, G219-G225.

- Hamdy, S., Rothwell, J. C., Brooks, D. J., Bailey, D., Aziz, Q. & Thompson, D. G. (1999b). Identification of the cerebral loci processing human swallowing with H₂¹⁵O PET activation. *Journal of Neurophysiology*, *81*, 1917-1926.
- Hamdy, S. (2006). Role of cerebral cortex in the control of swallowing. *GI Motility online*. Retrieved on 30.03.2009 from <http://www.nature.com/gimo/contents/pt1/full/gimo8.html>
- Hasegawa, Y., Kasai, T., Tsuji, T., & Yahagi, S. (2001). Further insight into the task-dependent excitability of motor evoked potentials in first dorsal interosseous muscle in humans. *Experimental Brain Research*, *140*, 387-396.
- Hauptmann, B., Skrotzki, A., & Hummelsheim, H. (1997). Facilitation of motor evoked potentials after repetitive voluntary hand movements depends on the type of motor activity. *Electroencephalography and Clinical Neurophysiology*, *105*(5), 357-364.
- Hess, C. W., Mills, K. R., & Murray, N. M. F. (1987). Responses in small hand muscles from magnetic stimulation of the human brain. *Journal of Physiology*, *388*, 397-419.
- Hooker, D. (1954). Early human fetal behaviour, with a preliminary note on double simultaneous fetal stimulation. *Research Publications - Association for Research in Nervous and Mental Disease*, *33*, 98-113.
- Holcomb, W.R. (2006). Effect of training with neuromuscular electrical stimulation on elbow flexor strength. *Journal of Sports Science and Medicine*, *5*, 276-281.
- Huckabee, M. L., Deecke, L., Cannito, M. P., Gould, H. J. & Mayr, W. (2003). Cortical control mechanisms in volitional swallowing: the Bereitschaftspotential. *Brain Topography*, *16*, 3-17.
- Huckabee, M. L., & Doeltgen, S. H. (2007a). Position Paper of the New Zealand Speech Therapists' Association (NZSTA) on Neuromuscular Electrical Stimulation in Dysphagia Management. Retrieved on 16.03.2009 from <http://www.speechtherapy.org.nz/information-for-speech-and-language-therapists>

- Huckabee, M. L., & Doeltgen, S. H. (2007b). Emerging Modalities in Dysphagia Rehabilitation: Neuromuscular Electrical Stimulation. *The New Zealand Medical Journal*, *120*, 1-9.
- Humbert, I. A., Poletto, C. J., Saxon, K. G., Kearney, P. R., Crujido, L., Wright-Harp, W., et al. (2006). The effect of surface electrical stimulation on hyolaryngeal movement in normal individuals at rest and during swallowing. *Journal of Applied Physiology*, *101*, 1657-63.
- Ikoma, K., Samii, A., Mercuri, B., Wassermann, E. M., & Hallett, M. (1996). Abnormal cortical excitability in dystonia. *Neurology*, *46*, 1371-1376.
- Ioannidis, J. P. A. (2005). Why most published research findings are false. *PLoS Med*, *2*, 124. retrieved from: 10.1371/journal.pmed.0020124
- Jasper, H. H. (1958). The ten-twenty electrode system of the International Federation. *Electroencephalography and Clinical Neurophysiology*, *10*, 370-375.
- Jean, A. (2001). Brain stem control of swallowing: neuronal network and cellular mechanisms. *Physiological Reviews*, *81*, 929-961.
- Kamen, G. (2004). Reliability of motor-evoked potentials during resting and active contraction conditions. *Medicine & Science in Sports & Exercise*, *36*, 1574-1579.
- Keel, J., Smith, M., & Wassermann, E. (2000). A safety screening questionnaire for transcranial magnetic stimulation. *Clinical Neurophysiology*, *112*, 720.
- Kern, M. K., Jaradeh, S., Arndorfer, R. C., & Shaker, R. (2001a). Cerebral cortical representation of reflexive and volitional swallowing in humans. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, *280*, G354-G360.
- Kern, M., Birn, R., Jaradeh, S., Jesmanowicz, A., Cox, R., Hyde, J. et al. (2001b). Swallow-related cerebral activity maps are not specific to deglutition. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, *280*, G531-G538.
- Kiger, M., Brown, C. S., & Watkins, L. (2006). Dysphagia Management: An analysis of patient outcome using VitalStim™ therapy compared to traditional swallow therapy. *Dysphagia*, *21*, 243-253.

- Kimberley, T. J., Scott, M. L., Auerbach, E. J., Dorsey, L. L., Lojovich, L. M., & Carey, J. R. (2004). Electrical stimulation driving functional improvements and cortical changes in subjects with stroke. *Experimental Brain Research*, *154*, 450-460.
- Kit-Lan, P. C. K. (1992). Contemporary trends in electrical stimulation: 'the frequency-specificity theory'. *Hong Kong Physiotherapy*, *13*, 23-27.
- Kleim, J. A., Chan, S., Pringle, E., Schallert, K., Procaccio, V., Jimenez, R. et al. (2006). BDNF val66met polymorphism is associated with modified experience-dependent plasticity in the human motor cortex. *Nature Neuroscience*, *9*, 735-737.
- Korfage, J. A., Schueler, Y. T., Brugman, P., & Van Eijden, T. M. (2001). Differences in myosin heavy-chain composition between human jaw-closing muscles and supra- and infrahyoid muscles. *Archives of Oral Biology*, *46*, 821-827.
- Kossev, A. R., Schrader, C., Dauper, J., Dengler, R., & Rollnik, J. D. (2002). Increased intracortical inhibition in middle-aged humans: a study using paired-pulse transcranial magnetic stimulation. *Neuroscience Letters*, *333*, 83-86.
- Leelamanit, V., Limsakul, C., & Geater, A. (2002). Synchronized electrical stimulation in treating pharyngeal dysphagia. *Laryngoscope*, *112*, 2204-2210.
- Leon-Sarmiento, F. E., Bara-Jimenez, W., & Wassermann, E. M. (2005). Visual deprivation effects on human motor cortex excitability. *Neuroscience Letters*, *389*, 17-20.
- Liepert, J., Uhde, I., Gräf, S., Leidner, O., & Weiller, C. (2001). Motor cortex plasticity during forced-use therapy in stroke patients: a preliminary study. *Journal of Neurology*, *248*, 315-321.
- Logemann, J.A. (1983). *Evaluation and treatment of swallowing disorders*. San Diego, CA: College-Hill Press.
- Logemann, J.A. (1997). *Evaluation and treatment of swallowing disorders* (2nd ed.). Austin, TX: Pro-Ed.

- Ludlow, C. L., Humbert, I., Saxon, K., Poletto, C., Sonies, B., & Crujido, L. (2007). Effects of surface electrical stimulation both at rest and during swallowing in chronic pharyngeal dysphagia. *Dysphagia*, 22, 1-10.
- Macaluso, G. M., Pavesi, G., Bonanni, M., Mancina, D., & Gennari, P. (1990). Motor-evoked potentials in masseter muscle by electrical and magnetic stimulation in intact alert man. *Archives of Oral Biology*, 35, 623-628.
- Maccabee, P. J., Amassian, V. E., Eberle, L. P., & Cracco, R. Q. (1993). Magnetic coil stimulation of straight and bent amphibian and mammalian peripheral nerve in vitro: locus of excitation. *Journal of Physiology*, 460, 201-219.
- Maeda, F., & Pascual-Leone, A. (2003). Transcranial magnetic stimulation: studying motor neurophysiology of psychiatric disorders. *Psychopharmacology*, 168, 359-376.
- Maertens de Noordhout, A., Rothwell, J. C., Day, B. L., Dressler, D., Nakashima, K., Thompson, P. D. et al. (1992). Effect of digital nerve stimuli on responses to electrical or magnetic stimulation of the human brain. *Journal of Physiology*, 447, 535-548.
- Malenka, R. C., & Nicoll, R. A. (1999). Long-term potentiation – a decade of progress? *Science*, 285, 1870-1874.
- Martin, S. E., Murray, G. M., Kemppainen, R., Masuda, Y., & Sessle, B. J. (1997). Functional properties of neurons in the primate primary motor cortex during swallowing. *Journal of Neurophysiology*, 78, 1516-1530.
- Martin, R. E., Goodyear, B. G., Gati, J. S., & Menon, R. S. (2001). Cerebral cortical representation of automatic and volitional swallowing in humans. *Journal of Neurophysiology*, 85, 938-950.
- Martin, R. E., MacIntosh, B. J., Smith, R. C., Barr, A. M., Stevens, T. K., Gati, J. S. et al. (2004). Cerebral Areas processing swallowing and tongue movement are overlapping but distinct: a functional magnetic resonance imaging study. *Journal of Neurophysiology*, 92, 2428-2493.
- Markram, H., Lubke, J., Frotscher, M., & Sakmann, B. (1997). Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science*, 275, 213-215.

- McConnel, F. M., Cerenko, D., Jackson, R. T., & Griffin, T. N. J. (1988). Timing of major events of pharyngeal swallowing. *Archives of Otolaryngology - Head & Neck Surgery*, *114*, 1413-1418.
- McConnell, K. A., Nahas, Z., Shastri, A., Lorberbaum, J. P., Kozel, F. A., Bohning, D. E. et al. (2001). The transcranial magnetic stimulation motor threshold depends on the distance from coil to underlying cortex: a replication in healthy adults comparing two methods of assessing the distance to cortex. *Biological Psychiatry*, *49*, 454-459.
- McDonnell, M. N., & Ridding, M. C. (2006). Afferent stimulation facilitates performance on a novel motor task. *Experimental Brain Research*, *170*, 109-115.
- McDonnell, M. N., Hilier, S. L., Miles, T. S., Thompson, P. D., & Ridding, M. C. (2007). Influence of combined afferent stimulation and task-specific training following stroke: a pilot randomized controlled trial. *Neurorehabilitation and Neural Repair*, *21*, 435-443.
- McKay, D., Brooker, R., Giacomini, P., Ridding, M. C., & Miles T. (2002a). Time course of induction of increased human motor cortex excitability. *Neuroreport*, *13*, 1271-1273.
- McKay, D., Ridding, M. C., Miles, T. S., & Thompson, P. D. (2002b). Induction of persistent changes in the organisation of the human motor cortex. *Experimental Brain Research*, *143*, 342-349.
- McMillan, A. S., Watson, C., & Walshaw, G. (1998a). Improved reproducibility of magnetic stimulation-evoked motor potentials in the human masseter muscle by a new method for locating stimulation sites on the scalp. *Archives of Oral Biology*, *43*, 665-668.
- McMillan, A. S., Watson, C., & Walshaw, G. (1998b). Transcranial magnetic-stimulation mapping of the cortical topography of the human masseter muscle. *Archives of Oral Biology*, *43*, 925-931.
- McMillan, A. S., Graven-Nielsen, T., Romaniello, A., & Svensson, P. (2001). Motor potentials evoked by transcranial magnetic stimulation during isometric and dynamic masseter muscle contraction in humans. *Archives of Oral Biology*, *46*, 381-386.

- Meilink, A., Hemmen, B., Seelen, H. A. M., & Kwakkel, G. (2008). Impact of EMG-triggered neuromuscular stimulation of the wrist and finger extensors of the paretic hand after stroke: a systematic review of the literature. *Clinical Rehabilitation*, 22, 291-305.
- Merton, P. A., & Morton, H. B. (1980). Stimulation of the cerebral cortex in the intact human subject. *Nature*, 285, 227.
- Meyer, B. U. (1992). *Magnetstimulation des Nervensystems*. Berlin: Springer.
- Miller, A. J. (1972). Significance of sensory inflow to the swallowing reflex. *Brain Research*, 43, 147-159.
- Miller, A. J. & Bowman, J. P. (1977). Precentral cortical modulation of mastication and swallowing. *Journal of Dental Research*, 56, 1154-1161.
- Miller, A.J. (1999). *The neuroscientific principles of swallowing*. San Diego, CA: Singular.
- Moonesinghe, R., Khoury, M. J., & Janssens, A. C. J. W. (2007). Most published research findings are false - but a little replication goes a long way. *PLoS Med* 4(2), e28 retrieved on 16.03.2009 from: 10.1371/journal.pmed.0040028
- Morrell, R. M. (1984). The neurology of swallowing. In M. E. Groher (Ed.) *Dysphagia: Diagnostic and Management* (pp. 3-36). Boston, MA: Butterworths.
- Mortifee, P., Stewaert, H., Schulzer, M., & Eisen, A., (1994). Reliability of transcranial magnetic stimulation for mapping the human motor cortex. *Electroencephalography and Clinical Neurophysiology*, 93(2), 131- 137.
- Mortimer, J. T. (1981). Motor prostheses. In: J. M. Brookhart, V. B. Mountcastle (Eds.), *Handbook of physiology: the nervous system* (2nd ed, pp. 155-187). Bethesda, MD: American Physiological Society.
- Muellbacher, W., Ziemann, U., Boroojerdi, B., Cohen, L., & Hallett, M. (2001). Role of the human motor cortex in rapid motor learning. *Experimental Brain Research*, 136, 431-438.

- Muellbacher, W., Richards, C., & Ziemann, U. (2002a). Improving hand function in chronic stroke. *Archives of Neurology*, *59*, 1278-1282.
- Muellbacher, W., Ziemann, U., & Wissel, J. (2002b). Early consolidation in human primary motor cortex. *Nature*, *415*, 640-644.
- Netter, F. H. (2006). *Atlas of Human Anatomy*. Philadelphia, PA: Saunders.
- Nudo, R. J., Wise, B. M., SiFuentes, F., & Milliken, G. W. (1996). Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science*, *272*, 1791-1794.
- Oh, B., Kim, D., & Paik, N. (2007). Recovery of swallowing function is accompanied by the expansion of the cortical map. *International Journal of Neuroscience*, *117*, 1215-1227.
- Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, *9*, 97-113.
- Oxford Dictionary of English. (2005). Revised Edition. C. Soanes, & A. Stevenson (eds). Oxford University Press.
- Park, C. L., O'Neill, P. A., & Martin, D. F. (1997). A Pilot study of oral electrical stimulation on swallow function following stroke: an innovative technique. *Dysphagia*, *12*, 161-166.
- Pascual-Leone, A., Grafman, J., & Hallett, M. (1994). Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science*, *263*, 1287-1289.
- Patton, H. D., & Amassian, V. E. (1954). Single- and multiple-unit analysis of cortical stage of pyramidal tract activation. *Journal of Neurophysiology*, *17*, 345-363.
- Peckham, P.H., & Knutson, J.S. (2005). Functional electrical stimulation for neuromuscular applications. *Annual Review of Biomedical Engineering*, *7*, 327-360.
- Peleg, G., & Goldman, J. A. (1978). Fetal deglutition: a study of the anencephalic fetus. *European Journal of Obstetrics, Gynecology and Reproductive Biology*, *8*, 133-136.

- Peinemann, A., Lehner, C., Conrad, B., & Siebner, H. R. (2001). Age-related decrease in paired-pulse intracortical inhibition in the human primary motor cortex. *Neuroscience letters*, *313*, 33-36.
- Penfield, W., & Jasper, H. H. (1954). *Epilepsy and the functional anatomy of the human brain*. Boston, MA: Little Brown.
- Perlman, A. L., & Christensen, J. (1997). Topography and functional anatomy of swallowing structures. In A. L. Perlman & K. Schulze-Delrieu (Eds.), *Deglutition and its Disorders*. San Diego, CA: Singular Publishing Group.
- Peurala, S. H., Pikaenen, J. S., Sivenius, J. & Tarkka, I. M. (2002). Cutaneous electrical stimulation may enhance sensorimotor recovery in chronic stroke. *Clinical Rehabilitation*, *16*, 706-716.
- Plowman-Prine, E. K., Triggs, W. J., Malcolm, M. P., & Rosenbek, J. C. (2008). Reliability of transcranial magnetic stimulation for mapping swallowing musculature in the human motor cortex. *Clinical Neurophysiology*, *119*, 2298-2303.
- Power, M., Fraser, C., Hobson A., Rothwell, J.C., Mistry, S., Nicholson, D.A., et al. (2004). Changes in pharyngeal corticobulbar excitability and swallowing behavior after oral stimulation. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, *286*, 45-50.
- Power, M. L., Fraser, C. H., Hobson, A., Singh, S., Tyrell, P., Nicholson, D. A. et al. (2006). Evaluating oral stimulation as a treatment for dysphagia after stroke. *Dysphagia*, *21*, 49-55.
- Pritchard, J. A. (1965). Deglutition by normal and anencephalic fetuses. *Obstetrics and Gynecology*, *25*, 289-297.
- Rattay, F., Resatz, S., Lutter, P., Minassian, K., Gilge, B., & Dimitrijevic, M.R. (2003). Mechanisms of electrical stimulation with neural prosthesis. *Neuromodulation*, *6*,(1), 42-56.
- Regan, D. (1989). *Human brain electrophysiology: evoked potentials and evoked magnetic fields in science and medicine*. New York: Elsevier.

- Reilly, J. P., Antoni H., Chilbert, M. A., Skuggevig, W., & Sweeney, J. D. (1992). *Electrical Stimulation and Electropathology* (p.6). Cambridge University Press.
- Requena, S. B., Puche, P. P., & Gonzalez-Badillo, J.J. (2005). Percutaneous electrical stimulation in strength training: an update. *Journal of Strength and Conditioning Research*, *19*, 438-448.
- Ridding, M. C., Taylor, J. L., & Rothwell, J. C. (1995). The effect voluntary contraction on cortico-cortical inhibition in human motor cortex. *Journal of Physiology*, *487*, 541-48.
- Ridding, M. C., Sheean, G., Rothwell, J. C., Inzelberg, R., & Kujirai, T. (1995). Changes in the balance between motor cortical excitation and inhibition in focal, task specific dystonia. *Journal of Neurology, Neurosurgery and Psychiatry*, *59*, 493-498.
- Ridding, M. C., Brouwer, B., Miles, T. S., Pitcher, J. B., & Thompson, P. D. (2000). Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects. *Experimental Brain Research*, *131*, 135-143.
- Ridding, M. C., & Taylor, J. L. (2001). Mechanisms of motor-evoked potential facilitation following prolonged dual peripheral and central stimulation in humans. *Journal of Physiology*, *537*, 623-631.
- Robbins, J., Levine, R.L., Maser, A., Rosenbek, J. C. & Kempster, G. B. (1993). Swallowing after unilateral stroke of the cerebral cortex. *Archives of Physical Medicine and Rehabilitation*, *74*, 1295-1300.
- Roesler, K. M., Hess, C. W., Heckmann, R., & Ludin, H. P. (1989). Significance of shape and size of the stimulating coil in magnetic stimulation of the human motor cortex. *Neuroscience letters*, *100*, 347-352.
- Roesler, K. M., & Magistris, M. R. (2008). The size of motor-evoked potentials: influencing parameters and quantification. In E. M. Wassermann, C. M. Epstein, U. Ziemann, V. Walsh, T. Paus & S. H. Lisanby (Eds). *The Oxford Handbook of Transcranial Stimulation*. New York: Oxford University Press.

- Rossini, P. M., Barker, A. T., Berardelli, A., Caramia, M. D., Caruso, G., Cracco, R. Q., et al. (1994). Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN Committee. *Electroencephalography and Clinical Neurophysiology*, *91*, 79-92.
- Rothwell, J. C., Thompson, P. D., Day, B. L., Boyd, S. & Marsden, C. D. (1991). Stimulation of the human motor cortex through the scalp. *Experimental Physiology*, *76*, 159-200.
- Rothwell, J. C. (1997). Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. *Journal of Neuroscience Methods*, *74*, 113-122.
- Rutecki, P. (1990). Anatomical, physiological and theoretical basis for the antiepileptic effect of vagus nerve stimulation. *Epilepsia*, *31*, S1-S6.
- Sandbrink, F. (2008). The MEP in clinical neurodiagnosis. In E. M. Wassermann, C. M. Epstein, U. Ziemann, V. Walsh, T. Paus & S. H. Lisanby (Eds). *The Oxford Handbook of Transcranial Stimulation*. New York: Oxford University Press.
- Sanes, J. N., & Donoghue, J. P. (1992). Organization and adaptability of muscle representations in primary motor cortex. In R. Caminiti, P. B. Johnson, & Y. Burnod (Eds). *Control of arm movement in space: neurophysiological and computational approaches* (pp. 103-128). Berlin: Springer.
- Satow, T, Ikeda, A., Yamamoto, J., Begum, T., Thuy, D., Matsushashi, M. et al. (2003). Role of primary sensorimotor cortex and supplementary motor area in volitional swallowing: a movement-related cortical potential study. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, *287*, G459-470.
- Sawaki, L., Wu, C. W., Kaelin-Lang, A., & Cohen, L. G. (2006). Effects of somatosensory stimulation on use-dependent plasticity in chronic stroke. *Stroke*, *37*, 246-247.
- Seyal, M., Mull, B., Bhullar, N., Ahmad, T. & Gage, B. (1999). Anticipation and execution of a simple reading task enhance corticospinal excitability. *Clinical Neurophysiology*, *110*, 424-429.

- Shaker, R., Ren, J., Zamir, Z., Sarna, A., Liu, J. & Sui, Z. (1994). Effect of aging, position, and temperature on the threshold volume triggering of pharyngeal swallows. *Gastroenterology*, *107*, 396-402.
- Shaker, R., Kern, M., Bardan, E., Taylor, A., Stewart, E.T., Hoffmann, R.G., et al. (1997). Augmentation of deglutitive upper esophageal sphincter opening in the elderly by exercise. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, *272*, G1518- G1522.
- Shaw, G. Y., Sechtem, P. R., Searl, J., Keller, K., Rawi, T. A., & Dowdy, E. (2007). Transcutaneous neuromuscular electrical stimulation (VitalStim) curative therapy for severe dysphagia: myth or reality? *Annals of Otolaryngology, Rhinology & Laryngology*, *116*, 36-44.
- Sheffler, L. R., & Chae, J. (2007). Neuromuscular electrical stimulation in neurorehabilitation. *Muscle & Nerve*, *35*, 562-590.
- Shribner, W. J. (1975). *A Manual of Electrotherapy* (4th ed.) Philadelphia, PA: Lea and Feboger.
- Slimp, J. C. (2004). Electrophysiologic intraoperative monitoring for spine procedures. *Physical Medicine & Rehabilitation Clinics North America*, *15*, 85-105.
- Smith, M. J., Keel, J. C., Greenberg, B. D., Adams, L. F., Schmidt, P. J., Rubinow, D. A. et al. (1999). Menstrual cycle effects on cortical excitability. *Neurology*, *53*, 2069-2072.
- Smith, M. J., Adams, L. F., Schmidt, P. J., Rubinow, D. R., & Wassermann, E. M. (2003). Abnormal luteal phase excitability of the motor cortex in women with PMS. *Biological Psychiatry*, *54*, 757-762.
- Stal, P. (1994). Characterization of human oro-facial and masticatory muscles with respect to fibre types, myosins and capillaries. Morphological, enzyme-histochemical, immuno-histochemical and biomechanical investigations. *Swedish Dental Journal Supplement*, *98*, 1-55.
- Stedman, A., Davey, N. J., & Ellaway, P. H. (1998). Facilitation of human first dorsal interosseous muscle responses to transcranial magnetic stimulation during voluntary contraction of the contralateral homonymous muscle. *Muscle & Nerve*, *21*, 1033-1039.

- Steele, C. M., Thrasher, A. T., & Popovic, M. R. (2007). Electric stimulation approaches to the restoration and rehabilitation of swallowing: a review. *Neurological Research, 29*, 9-14.
- Stefan, K., Kunesch, E., Cohen, L. G., Benecke, R., & Classen, J. (2000). Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain, 123*, 572-584.
- Stokes, M. G., Chambers, C. D., Gould, I. C., Henderson T. R., Janko, N. E., Allen, N. B. et al. (2005). Simple metric for scaling motor threshold based on scalp-cortex distance: application to studies using transcranial magnetic stimulation. *Journal of Neurophysiology, 94*, 4520-4527.
- Suiter, D. M., Leder, S. B., & Ruark, J. L. (2006). Effects of neuromuscular electrical stimulation on submental muscle activity. *Dysphagia, 21*, 50-60.
- Sumi, T. (1969). Some properties of cortically evoked swallowing in rabbits. *Brain Research, 15*, 107-120.
- Suzuki, M., Asada, Y., Ito, J., Hayashi, K., Inonue, H., & Kitano, H. (2003). Activation of cerebellum and basal ganglia on volitional swallowing detected by functional magnetic resonance imaging. *Dysphagia, 18*, 71-77.
- Terao, Y., & Ugawa, Y. (2002). Basic mechanisms of TMS. *Journal of Clinical Neurophysiology, 19*, 322-343.
- Thexton, A. J., Crompton, A. W., & German, R. Z. (2007). Electromyographic activity during the reflex pharyngeal swallow in the pig: Doty and Bosma (1956) revisited. *Journal of Applied Physiology, 102*, 587-600.
- Thompson, S. M., Mattison, H. A., & Nestor, M. W. (1999). Morphological correlates of long-term potentiation and depression. *Cellscience Reviews, 2*(2). Retrieved on 16.03.2009 from http://www.cellscience.com/reviews6/Morphological_correlates_LTP_LTD_memory.html
- Thompson, A. K., & Stein, R. B. (2004). Short-term effects of functional electrical stimulation on motor-evoked potentials in ankle flexor and extensor muscles. *Experimental Brain Research, 159*, 491-500.

- Toogood, J. A., Barr, A. M., Stevens, T. K., Gati, J. S., Menon, R. S., & Martin, R. E. (2005). Discrete functional contributions of cerebral cortical foci in voluntary swallowing: a functional magnetic resonance imaging (fMRI) "Go, No-Go" study. *Experimental Brain Research*, *161*, 81-90.
- Toyokura, M., Muro, I., Komiya, T., & Obara, M. (2002). Activation of pre-supplementary motor area (SMA) and SMA proper during unimanual and bimanual complex sequences: an analysis using functional magnetic resonance imaging. *Journal of Neuroimaging*, *12*, 172-178.
- VitalStim™, What is VitalStim therapy? Retrieved 27.02.2009 from http://www.vitalstimtherapy.com/what_is_vitalstim/index.aspx?id=148
- Wassermann, E. M., Greenberg, B. D., Nguyen, M. B., & Murphy, D. L. (2001). Motor cortex excitability correlates with an anxiety-related personality trait. *Biological Psychiatry*, *50*, 377-382.
- Wassermann, E. M. (2002). Variation in response to transcranial magnetic stimulation in the general population. *Clinical Neurophysiology*, *113*, 1165-1171.
- Wassermann, E. M. (2008). Inter- and intra-individual variation in the response to TMS. In E. M. Wassermann, C. M. Epstein, U. Ziemann, V. Walsh, T. Paus & S. H. Lisanby (Eds). *The Oxford handbook of transcranial stimulation*. New York: Oxford University Press.
- Woldag, H., Lukhaup, S., Renner, C., & Hummelsheim, H. (2004). Enhanced motor cortex excitability during ipsilateral voluntary hand activation in healthy subject and stroke patients. *Stroke*, *35*, 2556-2559.
- Wolters, A., Sandbrink, F., Schlottmann, A., Kunesch, E., Stefan, K., Cohen, L. G., et al. (2003). A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. *Journal of Neurophysiology*, *89*, 2339-2345.
- Wu, C. W., Seo, H. J. & Cohen, L. G. (2006). Influence of electric somatosensory stimulation on paretic-hand function in chronic stroke. *Archives of Physical Medicine and Rehabilitation*, *87*, 351-357.
- Youmans, S.R., & Stierwalt, J.A.G. (2006). Measures of tongue function related to normal swallowing. *Dysphagia*, *21*, 102-111.

- Zald, D. H., & Pardo, J. V. (1999). The functional neuroanatomy of voluntary swallowing. *Annals of Neurology*, 46,(3), 281-286.
- Ziemann, U., Corwell, B., & Cohen, L. G. (1998). Modulation of plasticity in human motor cortex after forearm ischemic nerve block. *The Journal of Neuroscience*, 18, 1115-1123.
- Ziemann, U., & Hallett, M. (2001). Hemispheric asymmetry of ipsilateral motor cortex activation during unimanual motor tasks: further evidence for motor dominance. *Clinical Neurophysiology*, 112, 107-113.
- Ziemann, U., Ilic, T. V., Alle, H., & Meitzschel, F. (2004). Cortico-motoneuronal excitation of three hand muscles determined by a novel penta-stimulation technique. *Brain*, 127, 1887-1898.

Appendices

Appendix 1. *Technical details of the electrical stimulator used in this research programme.*

Swallow Stimulator User's Manual

1.0 Introduction

The Swallow Stimulator is designed for research into the effect of electro-stimulation of swallowing. It interfaces with an existing EMG amplifier system (AD Instruments BioLab) which monitors the EMG. Based on the monitored EMG the Swallowing Stimulator detects an attempt to swallow and stimulates the swallowing muscles.

2.0 Setting Up

The output of the ADInstrument BioLab is connected to the INPUT connector on the rear of the Stimulator. The BioLab must be configured such that the expected EMG amplitude is amplified to 10-500mV.

The *STIMULATION* output is connected via the supplied cable to stimulation electrodes under the chin.

The *TRIGGER OUT* may be connected to a magnetic stimulator if desired.

Initially set the *STIM PERIOD* control to *OFF*.

Adjust the *THRESHOLD* control to achieve detection of the EMG. When EMG is detected the *LOCKOUT LED* (orange) will come on, and stay on for 10 seconds. Adjusting the *THRESHOLD* to a larger number means a greater magnitude EMG is required to trigger the stimulator, and conversely a smaller number means the stimulator is more sensitive to EMG.

Once reliable EMG detection is achieved set the *PERIOD* and *FREQUENCY* controls as desired. The *OUTPUT LED* (yellow) monitors the output and will be seen flashing at lower repetition rates, but appears essentially constant at the higher rates.

The *CURRENT* control should initially be set low (counter clockwise) and increased to obtain the desired effect. If insufficient stimulation effect is obtained ensure there is good electrical contact between the electrodes and the patient. A burning sensation at the electrode site may indicate poor contact.

After each stimulation period the stimulator is disabled for 10 seconds. This period is indicated by the *LOCKOUT LED*.

Caution

The stimulator outputs potentially dangerous voltages and currents.
 Use with adequate supervision.
 Only apply to peripheral muscles.
 Only for use in approved research studies with adequate consent.

Appendix 1 continued.

Swallow Stimulator User's Manual

Technical Description

Electrical:	Class I, Type BF Designed to meet AS/NZS3200.1.0
Power:	230V <100mA 400mA fuse
EMG Input	0 – 500mV
Trigger Output	5V pulse (>10ms) when EMG detected
Lockout	Detections disabled for 10s after successful detection
Stimulation Output	0 – 25mA (into 1K resistive load) Maximum current 50mA into short circuit Maximum voltage 220V into open circuit Source Impedance 500 Ω
Pulse Characteristics	200 μ s square pulse
Repetition Rate	1.25 / 2.5 / 5 / 10 / 20 / 40Hz / 80Hz
Duration	125ms / 250ms / 500ms / 1s / 2s / 4s
Overall size:	275 x 250 x 85 mm
Cleaning:	Use a clean, damp cloth Do not use harsh chemicals Do not immerse
Manufactured by	Medical Physics & Bioengineering Canterbury District Health Board Christchurch, NZ



Research Participants needed

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

**Effects of Electrical Stimulation on Nerve
 Transmission During Swallowing**

We are looking for healthy men and women
 aged 18-65 years

This study will take place at the Van der Veer Institute for Parkinson's and
 Brain Research, 66 Stewart St., Christchurch, New Zealand

This study includes 3 sessions of approximately 3hrs duration.
 You will be reimbursed for your travel expenses to and from the institute with
 NZ\$20 (Woolworths/ Countdown gift voucher) per session.
 If you are interested and would like more information, please contact

Sebastian Doeltgen

Dr. Maggie-Lee Huckabee

Phone: 03 378 6075
 Mobil: 0212 097 027
sebastian.doeltgen@web.de

Phone: 03 378-6070
 Mobil: 027 312 2305
maggie-lee.huckabee@canterbury.ac.nz

This project has been reviewed and approved by the Upper South A Regional Ethics Committee
 Advertisement Version 1, 28/09/07

<p>Swallowing Research Sebastian 378-6075 sebastian.doeltgen@web.de</p>	<p>Swallowing Research Sebastian 378-6075 or 0212 097 027 sebastian.doeltgen@web.de</p>	<p>Swallowing Research Sebastian 378-6075 sebastian.doeltgen@web.de</p>	<p>Swallowing Research Sebastian 378-6075 or 0212 097 027 sebastian.doeltgen@web.de</p>	<p>Swallowing Research Sebastian 378-6075 or 0212 097 027 sebastian.doeltgen@web.de</p>	<p>Swallowing Research Sebastian 378-6075 or 0212 097 027 sebastian.doeltgen@web.de</p>
---------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Appendix 3. *Transcranial Magnetic Stimulation (TMS) Adult Safety Screen*

Keel JC, July 2000

Transcranial Magnetic Stimulation[†] (TMS) Adult Safety Screen

<i>Name:</i>
<i>Date:</i>
<i>Age:</i>

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 4. *Edinburgh Handedness Questionnaire (Oldfield, 1971).***Handedness Questionnaire****Participant:****DOB:****Gender:****Age:*****Instructions***

Please indicate your preferences in the use of hands in the following activities.

If you are really indifferent, select "Either".

Where the preference is so strong that you would never try to use the other hand
select "No".

<i>When:</i>	<i>Which hand do you prefer?</i>			<i>Do you ever use the other hand?</i>	
<i>Writing</i>	<i>Left</i>	<i>Right</i>	<i>Either</i>	<i>Yes</i>	<i>No</i>
<i>Drawing</i>	<i>Left</i>	<i>Right</i>	<i>Either</i>	<i>Yes</i>	<i>No</i>
<i>Throwing</i>	<i>Left</i>	<i>Right</i>	<i>Either</i>	<i>Yes</i>	<i>No</i>
<i>Using Scissors</i>	<i>Left</i>	<i>Right</i>	<i>Either</i>	<i>Yes</i>	<i>No</i>
<i>Using a toothbrush</i>	<i>Left</i>	<i>Right</i>	<i>Either</i>	<i>Yes</i>	<i>No</i>
<i>Using a knife (without fork)</i>	<i>Left</i>	<i>Right</i>	<i>Either</i>	<i>Yes</i>	<i>No</i>
<i>Using a spoon</i>	<i>Left</i>	<i>Right</i>	<i>Either</i>	<i>Yes</i>	<i>No</i>
<i>Using a broom (upper hand)</i>	<i>Left</i>	<i>Right</i>	<i>Either</i>	<i>Yes</i>	<i>No</i>
<i>Striking a match</i>	<i>Left</i>	<i>Right</i>	<i>Either</i>	<i>Yes</i>	<i>No</i>
<i>Opening a box (lid)</i>	<i>Left</i>	<i>Right</i>	<i>Either</i>	<i>Yes</i>	<i>No</i>

QUESTIONNAIRE
Effect of muscle activation on Motor Evoked Potentials
of the floor of mouth muscles

Identifying number: _____

Which ethnic group do you belong to:

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

Do you suffer from the effects of any of the following medical problems:

- Stroke
- Nasal obstruction/history
- Heart Attack
- Asthma
- Chronic Obstructive Pulmonary Disorder (COPD)
- Swallowing difficulties
- Head and/or neck injury
- Head/ and/or neck surgery
- Neurological disorders (eg. Multiple Sclerosis etc.)
- Gastroesophageal Reflux Disease
- Paralysis of the diaphragm
- Chronic Fatigue Syndrome
- Do you have any other medical problems which you feel may impact on your ability to participate? Yes / No (Please circle one)

If yes, please describe

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

Yes / No (Please circle one)

If yes, please describe

Appendix 6.

Trial effects on MEP measures recorded during volitional contraction of submental muscles. Displayed are F-values and p-values.

Investigation	Measure	Baseline		5 post		30 post		60 post		90 post	
		F ^a	p	F ^a	P	F ^a	p	F ^a	p	F ^a	p
Effects of swallowing	Amplitude	0.436	0.96	0.576	0.88	0.602	0.859	0.956	0.502	1.547	0.104
	Latency	1.026	0.432	0.814	0.653	1.216	0.272	0.568	0.885	0.714	0.757
Effects of time	Amplitude	0.861	0.603	0.9	0.56	2.42	0.005	1.433	0.147	0.826	0.64
	Latency	0.986	0.471	0.491	0.934	0.676	0.794	0.837	0.628	1.56	0.1
5 Hz NMES	Amplitude	0.809	0.658	1.43	0.149	1.647	0.075	0.711	0.76	0.804	0.664
	Latency	0.328	0.989	0.476	0.942	1.444	0.143	0.81	0.657	0.585	0.873
20 Hz NMES	Amplitude	1.22	0.269	1.312	0.209	1.748	0.054	1.457	0.137	0.75	0.721
	Latency	0.975	0.483	1.715	0.06	0.876	0.586	0.843	0.621	1.195	0.287
40 Hz NMES	Amplitude	0.951	0.508	1.409	0.158	0.779	0.69	1.519	0.114	1.014	0.444
	Latency	1.583	0.093	0.892	0.569	0.689	0.782	1.437	0.146	1.339	0.194
80 Hz NMES	Amplitude	1.175	0.302	1.652	0.074	0.993	0.465	0.277	0.995	0.562	0.89
	Latency	0.738	0.733	0.538	0.906	1.004	0.454	0.727	0.744	1.076	0.385
20 repetitions	Amplitude	1.066	0.395	0.681	0.79	1.057	0.403	0.655	0.814	0.922	0.538
	Latency	1.447	0.141	0.652	0.817	1.569	0.097	0.586	0.872	0.653	0.816
60 repetitions	Amplitude	0.86	0.603	1.34	0.193	0.653	0.815	0.375	0.98	1.434	0.147
	Latency	1.608	0.086	1.282	0.227	0.898	0.563	1.17	0.307	0.593	0.867
Replication study	Amplitude	0.959	0.497	1.451	0.133	0.679	0.793	1.114	0.347	1.279	0.223
	Latency	1.378	0.167	1.871	0.031	1.352	0.181	0.831	0.635	0.846	0.619
Non-event-related NMES	Amplitude	1.084	0.374	1.256	0.238	0.918	0.541	1.463	0.128	0.604	0.86
	Latency	0.912	0.547	1.124	0.339	0.27	0.996	1.389	0.161	1.217	0.265
Continuous NMES	Amplitude	1.473	0.124	1.074	0.383	1.104	0.356	0.566	0.889	0.685	0.787
	Latency	1.691	0.06	1.05	0.406	0.982	0.474	1.051	0.405	1.562	0.093

Note. P < 0.05 displayed in bold. F^a: F_(14,126)

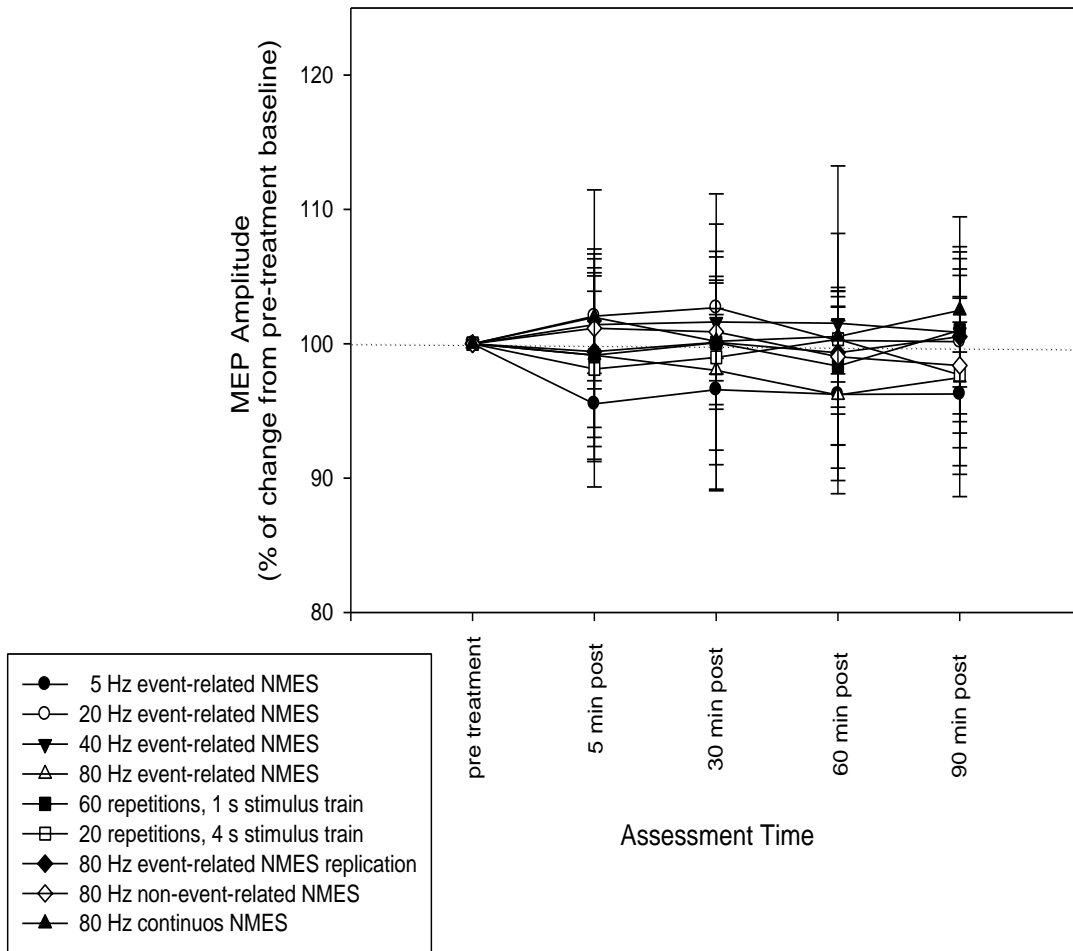
Appendix 7.

F-values and p-values of all statistical comparisons identifying the effects of "trial" on MEP measures recorded during volitional pharyngeal swallowing (VPS) within each block of 15 MEPs, recorded before and at four assessments after NMES treatment trials.

Investigation	Measure	Baseline		5 post		30 post		60 post		90 post	
		F ^a	p	F ^a	p	F ^a	p	F ^a	p	F ^a	p
Effects of swallowing	Amplitude	1.216	0.272	0.886	0.575	0.534	0.909	0.74	0.73	0.533	0.91
	Latency	0.819	0.647	0.746	0.725	0.607	0.855	0.546	0.901	0.935	0.524
Effects of time	Amplitude	1.257	0.244	0.639	0.828	0.988	0.469	0.681	0.79	0.997	0.46
	Latency	0.957	0.501	1.602	0.87	0.955	0.503	1.165	0.31	0.773	0.696
5 Hz NMES	Amplitude	1.309	0.216	1.242	0.258	0.556	0.892	1.328	0.205	1.33	0.204
	Latency	1.21	0.28	1.115	0.355	1.092	0.375	0.793	0.674	0.851	0.613
20 Hz NMES	Amplitude	1.561	0.104	1.108	0.36	0.735	0.734	1.04	0.421	0.645	0.821
	Latency	0.674	0.795	1.002	0.458	1.579	0.099	1.158	0.319	1.514	0.12
40 Hz NMES	Amplitude	1.214	0.278	0.792	0.675	0.742	0.728	1.116	0.354	0.706	0.764
	Latency	0.545	0.9	1.208	0.282	0.894	0.568	0.583	0.872	0.663	0.805
80 Hz NMES	Amplitude	1.368	0.183	0.631	0.834	0.864	0.6	1.066	0.398	8.32	0.633
	Latency	1.204	0.285	0.585	0.871	1.208	0.282	1.371	0.182	0.61	0.851
20 repetitions	Amplitude	0.585	0.871	1.098	0.369	0.7	0.77	1.659	0.077	1.331	0.203
	Latency	1.038	0.423	1.063	0.4	1.082	0.383	0.558	0.891	1.42	0.158
60 repetitions	Amplitude	0.672	0.796	1.935	0.031	1.162	0.316	1.089	0.377	1.065	0.398
	Latency	1.126	0.346	1.451	0.145	1.038	0.423	0.973	0.486	0.774	0.695
Replication study	Amplitude	1.001	0.457	0.635	0.832	1.609	0.085	0.616	0.847	1.052	0.408
	Latency	1.162	0.314	0.863	0.6	0.607	0.855	0.598	0.863	1.244	0.243
Non-event-related NMES	Amplitude	1.23	0.262	0.994	0.463	1.016	0.442	0.959	0.499	1.66	0.072
	Latency	1.019	0.439	0.992	0.466	0.858	0.606	1.449	0.14	0.506	0.926
Continuous NMES	Amplitude	0.94	0.519	1.691	0.065	8.52	0.611	0.907	0.553	0.745	0.726
	Latency	1.617	0.083	0.572	0.882	1.333	0.197	1.185	0.294	0.565	0.887

Note. P < 0.05 displayed in bold. F^a: F_(14,126)

Appendix 8. *Changes in MEP onset latency, recoded during the VC muscle pre-activation condition, in response to all NMES treatment protocols, relative to pre-treatment baseline. Error bars represent SD. Note. * $p < 0.05$.*



Appendix 9. Changes in MEP onset latency, recorded during the VPS muscle pre-activation condition, in response to all NMES treatment protocols, relative to pre-treatment baseline. Error bars represent SD. Note. * $p < 0.05$.

