

Closed-loop stimulation for upper limb rehabilitation following spinal cord injury and stroke

Edmund Francis Hodkin

Thesis submitted for the Degree of
Doctor of Philosophy

Institute of Neuroscience
Faculty of Medical Sciences
Newcastle University
Newcastle upon Tyne, UK

Supervisors:

Prof Andrew Jackson

Prof Helen Rodgers

October 2018



Abstract

Innovation is required to improve upper limb rehabilitation for neurological conditions such as stroke and spinal cord injury (SCI). There is growing appreciation of the importance of neural plasticity in recovery, and how this can be facilitated by synchronous activity in peripheral neural circuits and central brain areas. However, despite increasing scientific evidence, technological solutions that exploit associative plasticity have not yet been widely evaluated in clinical practice.

In this thesis, I report the development and initial evaluation of a novel device which enabled a reaching and grasping motion in the affected limb by combining assistive functional electrical stimulation (FES) with inferred voluntary brain activity. The device was designed to enable translation from laboratory-to-clinic by overcoming common practical barriers to translational research, such as adaptability and ease of use.

The device was demonstrated to be usable by individuals with either chronic stroke or SCI, and received positive qualitative feedback. Some participants showed modest improvements on assessments of upper limb function following a short intervention period.

A study with healthy able-bodied volunteers indicated that after using the device, corticospinal pathways to the antagonist (flexor) muscle may be facilitated, and this facilitation might be increased by adjusting the relative timing of stimulation and inferred brain activity.

The device could also deliver alternative stimulation techniques, and an exploratory study into transcutaneous spinal cord stimulation (tSCS) was conducted with healthy able-bodied volunteers. It was found that tSCS may activate peripheral and spinal pathways within acceptable comfort levels, but the parameters used in this study did not to generate functional contractions. An unexpected oscillatory motor response provided insights into how tSCS acts upon the motor system.

Prior to a large scale evaluation of clinical effectiveness, further research is required to: further develop a theoretical basis for the intervention; demonstrate the mechanisms of action; and to evaluate the efficacy of the device.

Acknowledgements

In addition to the acknowledgements found at the start of each chapter and the ‘Statement on Collaborative Work’ on the next page, I would like to thank all those involved in this thesis. In no particular order, this includes (but is not limited to): everybody at the Miami Project to Cure Paralysis, in particular, Monica Perez and Yuming Lei for support their support and hospitality; everybody at the Institute of Neurosciences, Kolkata (I-NK), in particular, Robin Sengupta, Hrishikesh Kumar, Supriyo Choudhury, Ravi Singh, Ummatul Siddique and Simin Rahman; Stuart Baker for making introductions to both the Miami Project and I-NK, offering expertise and advice, as well as sitting on my review panel; Anna Basu for also sitting on my PhD review panel and offering useful insights; everyone at the Institute of Neuroscience at Newcastle University, for making the daily life possible, this includes Ann Fitchett, Beckie Hedley and Glynis Mitchinson; the Stroke Research Group, including Helen Bosomworth, Sarah Moore and Chris Price; Mark Baker for his support and advice; Norman Charlton and Joe Wardle, for their engineering expertise, help and guidance; everybody in motor group and Jackson lab, this includes Wei Xu, Damar Susilaradeya, Felipe De Carvalho, Thomas Guiho, Matthieu Ambroise, Thomas Hall, Boubker Zaaïmi, Peter Trebilcock, Alex Clarke, Riashad Foysal, Roger Whittaker, and Demetris Soteropoulos; Isabel Glover for her support at I-NK, and insights, ideas and comments throughout; Colin Wan, George Evans and Jonathan Humby for their hard work during their master’s project and for their contribution to this thesis; and finally, I would like to thank my supervisors Andrew Jackson and Helen Rodgers for their help and support, for creating an environment to conduct this work, and for their patience reading this manuscript.

Away from academia, I would like to thank everybody who has support me throughout this process.

Funding

Many thanks to the funders who supported the research contained in this thesis:

- Wellcome Trust, postgraduate research studentship (2015 to 2018)
- EPSRC Preparing for GCRF Award (PI: Dr Andrew Jackson) - Low cost rehabilitation of hand function following stroke (2016 to 2017)

Statement on Collaborative Work

Over the course of my PhD, I have been fortunate to work with a number of other students, and they made significant contributions to the work presented in this thesis. Some of this work has subsequently been reported in their master's theses. In addition to acknowledgements at the start of each chapter, here, I endeavour to make clear my independent contribution and where overlaps exist.

1. Colin Wan (MRes student), Newcastle University – Colin contributed to two chapters in this thesis. He collected data for two participants in the extended intervention presented in Chapter 4, Section 4.3. As one individual was unable to complete the intervention, he reported this dataset as a case study in his master's thesis. Following training, Colin was responsible for data collection, and under my supervision he completed his own analysis and discussion. This extended intervention dataset was furthered by Ummatul Siddique and Simin Rahman – see below.

Secondly, Colin was responsible for recruitment and data collection for the study presented in Chapter 5 ('Investigations into the mechanism of action of the novel device in healthy able-bodied participants'). I initiated this project, designed the study, programmed experiments, and provided Colin with code for completing data analysis. Colin contributed to the design of the 'delayed' stimulation intervention. Under my guidance, Colin completed his own analysis and discussion, as presented in his MRes thesis. I have re-analysed this dataset in this thesis, including: analysis of individual datasets and baseline EMG. The discussion and interpretation of results are all my own.

2. Ummatul Siddique and Simin Rahman (Master's students), Institute of Neurosciences, Kolkata (I-NK) / Amity University, Noida. Ummatul and Simin were master's students visiting I-NK. They collected a dataset for the extended intervention presented in Chapter 4, Section 4.3. Alongside the team at I-NK, they were responsible for recruitment and data collection. With my guidance, Ummatul analysed and reported the dataset collected at I-NK in her master's dissertation. I was responsible for initiating the project, the study design and training. I later combined the datasets collected by Ummatul, Simin and Colin (see above) and it is this combined dataset that is reported in this thesis.

3. George Evans (MRes student), Newcastle University – George made significant contributions to the dataset presented in Chapter 6 (‘An exploration of transcutaneous spinal cord stimulation for applications in upper limb rehabilitation’). I initiated the project, and with input from Mark Baker and Andrew Jackson, George and I developed the study presented in this thesis. I was responsible for writing all of the scripts and code for data collection. George completed recruitment and data collection, and his own analysis, in part, using analysis scripts I provided for him. His analysis and discussion of the results are presented in his MRes thesis. I reanalysed the dataset, including the bootstrap statistical testing presented in this thesis. The interpretation and discussion of these results are all my own.
4. Jonathan Humby (MRes student), Newcastle University – Jonathan Humby contributed to the feasibility study dataset presented in Chapter 4, Section 4.2. I designed the study, and following training by me, and with the support of the team at I-NK, Jonathan recruited participants and completed data collection. Under my guidance, he presented this dataset in his MRes thesis. I later combined his dataset with feasibility study data collected by myself and Isabel Glover (see below), and the output of this is presented in Chapter 4, Section 4.2. Jonathan was also a co-author on the paper Hodkin et al. [1].
5. Isabel Glover (PhD student), Newcastle University – Isabel Glover collected a dataset for the feasibility study presented in Chapter 4, Section 4.2 She did not complete any further formal analysis, except for her role as a co-author on the corresponding publication (Hodkin et al. (2018)). Isabel also contributed to collecting the views of stroke survivors at I-NK, see Chapter 2, Section 2.5. She did not complete any analysis of this dataset.
6. Yuming Lei (Post-doc), University of Miami – Yuming supported my work at the Miami Project to Cure Paralysis at the University of Miami. Yuming recruited participants, and together we delivered the intervention. I was responsible for analysis and discussion of this dataset, with Yuming contributing as co-author on our publication Hodkin et al. [1].

Publications

Papers:

E. F. Hodkin, Y. Lei, J. Humby, I. S. Glover, S. Choudhury, H. Kumar, M. A. Perez, H. Rodgers, and A. Jackson, “Automated FES for Upper Limb Rehabilitation Following Stroke and Spinal Cord Injury,” *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 26, no. 5, pp. 1067-1074, 2018.

Conferences:

The contents of this thesis have been presented in various forms at the following conferences:

- UK Sensory-Motor Conference, Newcastle upon Tyne, 2016
- NeuroPalooza Conference, Newcastle upon Tyne, 2016
- IMechE Engineering the Upper Limb Conference, London, 2016
- UK Sensory-Motor Conference, Bristol, 2017
- Society for the Neural Control of Movement (NCM), Dublin, 2017
- Rehab Week / IFESS, London, 2017
- Society for Neuroscience (SfN), Washington DC, 2017
- Postgraduate Symposium, Newcastle upon Tyne, 2018

Other Works:

E. F. Hodkin, “A synergy in scientific research: the I-NK collaboration”, *React Magazine*, issue 11, pp. 23-24, 2018.

Table of contents

Abstract.....	3
Acknowledgements	5
Funding	5
Statement on Collaborative Work.....	7
List of figures.....	13
List of tables.....	15
Abbreviations	17
1. Introduction and background.....	19
1.1 Introduction	20
1.2 Current approaches to rehabilitation	21
1.3 New approaches to rehabilitation.....	24
1.4 This thesis.....	33
2. Development of a closed-loop device for rehabilitation following stroke and SCI.....	35
2.1 Introduction	37
2.2 Design considerations	37
2.3 Prototypes.....	40
2.4 The final device.....	43
2.5 User group feedback.....	47
2.6 Future designs	49
3. Investigations into the utility of the device for upper limb rehabilitation following spinal cord injury.....	51
3.1 Introduction	53
3.2 Methods.....	53
3.3 Results	55
3.4 Discussion	58
3.5 Conclusion.....	60
4. Investigations into the utility of the device for upper limb rehabilitation following stroke.....	61
4.1 Introduction	63
4.2 A feasibility study to investigate usability and possible benefits of using the device following stroke.....	64
4.3 An extended study to investigate the possible accrument of functional benefits with a longer intervention.....	68

4.4	A study to investigate the utility of the device when stimulation is delivered during a rest period vs. delivery concurrent with movement	76
4.5	Analysis of combined data from the above studies to assess changes observed in a larger sub-population of stroke survivors.....	84
4.6	Conclusions	86
5.	Investigations into the mechanism of action of the novel device in healthy able-bodied participants.....	89
5.1	Introduction	91
5.2	Methods.....	92
5.3	Results	98
5.4	Discussion	106
5.5	Conclusion.....	114
6.	An exploration of transcutaneous spinal cord stimulation for applications in upper limb rehabilitation	115
6.1	Introduction	117
6.2	Methods.....	117
6.3	Results	123
6.4	Discussion	135
6.5	Conclusion.....	141
7.	General discussion: A novel approach to upper limb rehabilitation following spinal cord injury and stroke	143
7.1	Overview	144
7.2	Translational pipeline.....	146
7.3	A closed loop?.....	147
7.4	The future of FES.....	148
7.5	Further studies.....	150
7.6	Summary	151
8.	References.....	153

List of figures

1.1	A simplified diagram of the motor system for controlling an upper limb muscle	25
1.2	Three different protocols for inducing Hebbian plasticity	30
2.1	A prototype bimanual closed-loop task	40
2.2	A two-sided pulley for a closed-loop FES task	41
2.3	A uni-manual block moving task	42
2.4	The device developed for this thesis	43
2.5	A system schematic for the device	44
2.6	The closed-loop created by the device, stimulator, controller and participant	45
2.7	The intervention protocol	46
2.8	A selection of the qualitative data collected from the physiotherapist focus group	48
2.9	Two devices combined in a modular fashion to create a pulley system	50
3.1	Individual ARAT scores for the trained and untrained sides before and after the intervention	57
3.2	The mean change in ARAT score for the trained and untrained sides	57
3.3	A selection of the qualitative data	58
4.1	ARAT scores for participants in this feasibility study	66
4.2	A selection of the structured qualitative feedback	67
4.3	The intervention and assessment timings for the extended intervention	69
4.4	Changes in ARAT score	72
4.5	Change in Fugl Meyer upper extremity function score	72
4.6	Change in Fugl Meyer upper extremity passive range of motion (ROM) score	73
4.7	Change in Fugl Meyer upper extremity sensation score	73
4.8	Change in ArmA Section A score	74
4.9	Change in ArmA Section B score	74
4.10	The timing of the intervention and assessments in this study	77

4.11	The ‘stimulation during rest’ condition	78
4.12	A comparison of the changes in ARAT score observed in the two conditions tested	81
4.13	The combined average change in ARAT score during either intervention vs. baseline	81
4.14	A selection of qualitative feedback collected during the study	82
4.15	The average change in ARAT score following 2 weeks of training with participants grouped by initial ARAT score	86
5.1	An overview of the reaching phase of the task for the four conditions used in this study	92
5.2	An overview of the protocol used throughout this chapter	93
5.3	The TMS set-up used in this study	94
5.4	The protocol used to compare changes in corticospinal excitability with and without FES delivered during the intervention	95
5.5	The protocol used to investigate changes in corticospinal excitability induced by stimulation delivered in two bursts during the rest period between trials	95
5.6	The ‘delayed stimulation’ condition	96
5.7	Average change in MEP size in the ‘no stimulation’ and ‘stimulation with movement’ conditions following the intervention	99
5.8	Individual changes in MEP size following the ‘no stimulation’ intervention	100
5.9	Individual changes in MEP size following the ‘stimulation with movement’ intervention	100
5.10	Average change in MEP size following the ‘stimulation during rest’ and ‘stimulation with movement’ interventions	101
5.11	Individual changes in MEP size following the ‘stimulation during rest’ intervention	102
5.12	Average change in MEP size following the ‘delayed stimulation’ and ‘stimulation with movement’ interventions	103
5.13	Individual change in MEP size following the ‘delayed stimulation’ intervention	104
5.14	The percentage change of baseline EMG activity relative to pre-intervention values during the ‘no stimulation’ and ‘stimulation with movement’ conditions	105
5.15	The percentage change of baseline EMG activity relative to pre-intervention values during the ‘delayed stimulation’ and the ‘stimulation during rest period’ conditions	105

6.1	A schematic diagram to show approximate electrode positions used in this study	118
6.2	The three different types of stimulation used during this study	119
6.3	The stimulation protocol used for this tSCS study	120
6.4	An example of the bootstrap statistical method used for data analysis	122
6.5	The average current required at resting motor threshold for each stimulation type	124
6.6	The average motor evoked response, of the muscle identified at threshold for the 'single' stimulation type, as a proportion of its response to 'conventional' stimulation	124
6.7	The average comfort scores for all participants	126
6.8	The effect of stimulation duration on comfort score	126
6.9	The average comfort score for increasing intensity	127
6.10	An example of oscillatory behaviour	129
6.11	An example oscillatory behaviour at a range of frequencies	129
6.12	An example of strong oscillations across multiple muscles	130
6.13	The output of bootstrap statistical testing of EMG collected during the first 0.5s stimulation train at each test frequency (20, 50, 100Hz) for each stimulation type ('conventional', 'burst', 'single')	131
6.14	The output of bootstrap statistical testing of the EMG signals collected for 0.5s trains of 'conventional' stimulation at intensities 90 to 140% of resting motor threshold	132
6.15	A plot showing the a-synchronous behaviour of two oscillations	133
6.16	The oscillatory motor response to peripheral nerve stimulation	133
6.17	The oscillatory motor response to a gentle contraction	134
6.18	The oscillatory motor response to tSCS controlled by a Poisson process	134

List of tables

3.1	Participants in this study	56
4.1	Participants in this study	65
4.2	Participants in this study	71
4.3	Participants in this study	80
4.4	Participant reported comments and observation from the study	83

Abbreviations

ADL	Activity of Daily Living
APB	Abductor Pollicis Brevis
ARAT	Action Research Arm Test
ArmA	Arm Activity Measure
ASIA	American Spinal Injury Association
BCI	Brain-Computer Interface
C-	Cervical, i.e. C5 is the 5 th spinal cord cervical level
CIMT	Constraint-induced movement therapy
CNS	Central Nervous System
CPG	Central Pattern Generator
EDC	Extensor Digitorum Communis
EEG	Electroencephalography
EMG	Electromyography
EPSP	Excitatory Postsynaptic Potential
FDI	First Dorsal Interosseous
FDS	Flexor Digitorum Superficialis
FES	Functional Electrical Stimulation
FMA	Fugl Meyer Assessment
IMU	Inertial Measurement Unit
I-NK	Institute of Neurosciences, Kolkata
L-	Left hand side
LTD	Long-term Depression

LTP	Long-term Potentiation
MCID	Minimal Clinically Important Difference
MEP	Motor Evoked Potential
NHS	National Health Service
NLI	Neurological Level of Injury
NMJ	Neuromuscular Junction
PAS	Paired Associative Stimulation
PD	Parkinson's Disease
PNS	Peripheral Nervous System
R-	Right hand side, i.e. R-APB is the Right hand APB muscle
S-	Sacral, i.e. S4 is the 4 th spinal cord sacral level
SCI	Spinal Cord Injury
SCIM	Spinal Cord Injury Measure
SCS	Spinal Cord Stimulation
TMS	Transcranial Magnetic Stimulation
tDCS	Transcranial Direction Current Stimulation
TENS	Transcutaneous electrical nerve stimulation
tSCS	Transcutaneous Spinal Cord Stimulation

Chapter 1

Introduction and background

Key points:

- There is a clear need for innovation in the field of upper limb rehabilitation for stroke and spinal cord injury to improve recovery
 - Traditional methods have limited benefit, but emerging technologies centred on driving neural plasticity using a closed-loop system have shown promise
 - In addition, to be introduced into widespread clinical practice, these new technologies must offer flexibility, be user-friendly and affordable
-

1.1 Introduction

Acquired disability following acute neurological conditions, such as stroke and spinal cord injury (SCI), is a global challenge [2-4]. A stroke is caused by a loss of blood supply to a region of brain, leading to cell death, while a SCI occurs when either through traumatic (e.g. a car accident) or non-traumatic (e.g. infection or compression) events the spinal cord is damaged. In both instances the nervous system is disrupted, which can lead to long-term disability, including reduced voluntary control of movement, shortening and weakening of muscles, spasticity, and sensory and proprioceptive deficits.

With a combined annual incidence of stroke in the USA and the UK approaching 1 million [5, 6], and India being described as having a stroke epidemic [7], rehabilitation is crucial for maintaining the health and well-being of society. Three quarters of people suffering an acute stroke report upper limb weakness [8], with 45% having limited fine hand use 18 months after stroke [9]. Improving arm function is a research priority for stroke survivors, caregivers and health professionals [10], and despite many dedicated and highly-skilled research groups, the 2014 Cochrane Review ('Interventions for improving upper limb function after stroke') [11] stated that no high-quality evidence could be found for any current upper limb rehabilitation interventions.

In the UK, there are an estimated 40,000 people living with SCI [12], and a further 282,000 in the USA [13]. Combined, it is estimated that there are 18,000 new cases in the UK and USA each year [12, 13]. Incomplete tetraplegia, where all four limbs are affected, is the most common form of SCI, and regaining hand and arm use is ranked as the highest priority amongst tetraplegics [14].

In this chapter, I will firstly give a brief overview of upper limb impairment following stroke and SCI, and existing approaches to upper limb rehabilitation. Secondly, I will outline novel therapeutic techniques and approaches emerging from the field of neuroscience, and highlight the opportunities for innovation in this field. Finally, I will describe how this thesis is structured to introduce a novel technology developed for upper limb rehabilitation following stroke and SCI.

1.2 Current approaches to rehabilitation

1.2.1 Disability following stroke and SCI

The degree of upper limb impairment following stroke and SCI is diverse. A stroke is the result of a loss of blood supply to the brain either caused by a blockage (ischaemic ~80%) or a bleed (haemorrhage ~20% [2]). This can lead to cell death in the cortex, as well as subcortical areas such as the brain stem and the cerebellum, according to the vascular territory affected. The consequence of this, can be a loss voluntary control of the upper limb, leading to limb weakness and subsequently muscle atrophy, contracture, shoulder subluxation and spasticity. Furthermore, sensory and proprioceptive deficits can lead to a loss of awareness of limb position [11].

Tetraplegia occurs when cervical spinal cord segments (C1-C8) are damaged leading to impairments in all four limbs. This impairment can range from ‘Complete’ where there is a loss of sensory and motor function below injured segment, and is defined as when no sensory or motor function is preserved in sacral segments S4-S5, through to ‘Sensory Incomplete’, ‘Motor Incomplete’ and ‘Normal’. These categories are classified as ASIA-A through to ASIA-E on the American Spinal Association scale [15, 16].

Voluntary control of upper limb movements is impaired dependent on the level of injury, such that a C4 injury results in the retention of moderate strength in the elbow flexor and deltoid muscles only. A greater strength in elbow flexors is maintained with a C5 injury, and further strength is typically available at subsequent lower levels: active wrist extension at C6, elbow extension at C7, and strength in finger flexors at C8 [15]. This loss of voluntary control leads to reduced limb activity resulting in muscle atrophy, muscle contractures, and pain. It has been suggested that spasticity may also, in part, be caused by mechanical changes in the muscle due to this reduction in movement [17]. Research has also indicated that following SCI supraspinal structures such as the motor cortex undergo change [18].

1.2.2 Current rehabilitative methods

Rehabilitation following stroke is typically thought of as being delivered by a multidisciplinary team including physiotherapists and occupational therapists using traditional methods such as: stretching and positioning; ‘hands on’ therapy during which a therapist assists the person in making movements; strength training; and task specific training, where an activity of daily living (ADL) may be practiced. However, despite many years of implementation, a comprehensive review of upper limb rehabilitation following stroke found either low grade

evidence, a lack of evidence or moderate evidence of no benefit or harm for all of these interventions [11].

Importantly, this review sign-posted promising avenues of investigation (i.e. those with moderate-quality evidence) that included: constraint-induced movement therapy (CIMT) or ‘forced use therapy’, during which the less affected limb is restricted from being used; unilateral training (versus bilateral training); mental practice, which is often combined with subsequent physical practice; mirror-therapy; repetitive training (dose > 20 hours); and robotics, which may be used to deliver enhanced repetitive training. Additionally, sensory interventions and virtual reality were also found to have moderate evidence of benefit.

A common theme can be observed amongst these encouraging interventions. They typically engage the brain and subsequently pair it with either simulated (mirror-therapy, virtual reality) or actual movement of the affected limb (CIMT, robotics, repetitive training, mental practice followed by physical movement, unilateral training). As discussed below, this is in line with a concept known as Hebbian plasticity, and is supported by the latest research from the field of neuroscience.

Rehabilitation of the upper limb following a SCI focuses on the early introduction of passive exercises and positioning of joints to prevent muscle atrophy, joint contractures, stiffness and reducing pain [15]. Additionally, muscle strengthening is important for independent transfers from bed or a wheelchair [15]. Rehabilitation not only aims to promote recovery, but also compensation and adaptation, such as training individuals with wrist strength, but no finger or thumb control, to use the tenodesis grip [19]. Unfortunately, these techniques only result in limited improvements and there is a need to develop new treatments [15, 20-22], with research groups aspiring to strengthen spared neural networks through neuroplasticity to improve active function and control [18, 20, 23-25]. Systematic reviews of clinical trials are not as abundant for SCI as for stroke, but there is positive evidence of clinical effectiveness for high intensity training, augmented feedback and virtual reality training for locomotion, and some evidence for training duration, augmented feedback and virtual reality training for hand function [20]. Like stroke, it is anticipated that neuroplasticity is key to overcoming damage to the nervous system [20, 24]

1.2.3 Intensity and a ‘critical window’

The time-period following a stroke is typically divided into stages known as acute (<1 week), sub-acute (1 week to 6 months) and chronic (>6 months) to reflect the evolution of the

condition following initial onset [26]. The 1994 Copenhagen Stroke Study stated that stroke survivors with mild and severe upper-extremity paresis should not expect recovery of upper extremity function after 6 and 11 weeks respectively [27]. This promoted the idea of a ‘critical window’ for recovery, which has been widely accepted and demonstrated in animal studies [28]. However, while this may be the optimum period for recovery, studies have since shown that large amounts of therapy can result in better outcomes for stroke survivors with upper limb impairment beyond 2-3 months [29, 30].

The case for large amounts of therapy is furthered by increasing evidence that the dosage (i.e. frequency and intensity of rehabilitation sessions) is critical for successful rehabilitation [31-33] and that at present the dosage received by people is small (23 to 32 repetitions per session) compared to those tested in animal models (400 reaches per day) [28, 31, 34, 35]. This has led to stroke survivors being described as ‘inactive and alone’ [36], a confounding factor in poor rehabilitative outcomes [36, 37].

The time periods used to define key pathological events following SCI are: early acute (≤ 48 hours), secondary subacute (≤ 14 days), intermediate (≤ 6 months) and chronic (≥ 6 months) [38]. A critical therapeutic window has not been defined for SCI, although following the acute phase, evidence suggests that earlier interventions may be beneficial [20]. Most recovery of sensorimotor deficits occurs over the first 3 to 4 months, but training can induce changes at later stages [20].

Therefore, it is suggested that new approaches to upper limb rehabilitation should facilitate an increase in the amount of therapy received and promote mobilisation of the affected limb at an appropriate time soon after injury.

1.2.4 Behavioural restitution vs. compensation

A recent taskforce on rehabilitation following stroke described the terminology associated with the field as “*problematic, vague and an impediment to progress*” [26]. They subsequently defined rehabilitation as “*a process of care*”, whilst recovery is the “*extent to which body structure and functions, as well as activities, have returned to their pre-stroke state*”. A further distinction was then made between two approaches to recovery. The first is *compensation*, where goals are accomplished through substitution of a pre-stroke methodology with a new approach. This may require assistive tools and devices, such as a wheelchair or a walking stick. The other is *behavioural restitution* leading towards *true recovery*. Here, behavioural

restitution is defined as “*a return towards more normal patterns of motor control...*” and “*the process towards true recovery*”. True recovery is the “*return of some or all of the normal repertoire of behaviours that were available before injury*”, and importantly, neural repair is required for true recovery [26].

While compensation and the use of assistive devices is an important aspect of rehabilitation, true recovery must be the ultimate goal for research groups working in the field of neuroscience, and as such, the following section explores how advances in the field of neurorehabilitation may allow researchers to harness properties of the nervous system to work towards true recovery following stroke and SCI.

1.3 New approaches to rehabilitation

1.3.1 The motor system

Prior to a discussion on new approaches to the neural repair, it is important to briefly consider how the motor system controls the upper limb, and where interventions could target the nervous system to improve upper limb function. A simplified diagram of the pathways controlling an upper limb muscle is shown in Figure 1-1. For clarity, much of what is known about the motor system and different pathways has been omitted, for example, the reticular spinal tract and polysynaptic projections to lower motor neurons are not shown. A thorough review of descending pathways in motor control can be found in Roger Lemon’s seminal work ‘Descending Pathways in Motor Control’ [39].

In healthy able-bodied individuals, the motor cortex is the region of the brain that sends voluntary commands to the spinal cord, where they may undergo further processing, before being propagated to a muscle to generate a contraction. The ‘butterfly’ shaped region in the centre of the spinal cord contains grey matter, such as cell bodies of motor neurons and interneurons, and the outer region contains myelinated axons and glial cells, known as white matter.

In addition to the cortex, the spinal cord receives sensory input from the peripheral nervous system through afferent pathways, which enter the cord via the dorsal roots. An example of these sensory inputs are the Group Ia afferents, which detect the rate of change of muscle length through a receptor known as a muscle spindle. Afferent inputs can have monosynaptic and polysynaptic inputs to lower motor neurons, therefore generating movements without conscious input, a process known as a reflex.

Any damage to the pathway from cortex to muscle, can lead to an impaired ability to generate voluntary movement. Furthermore, damage to the spinal cord may lead to impairment at spinal levels below the site of injury, as both ascending and descending commands to and from supraspinal structures are interrupted.

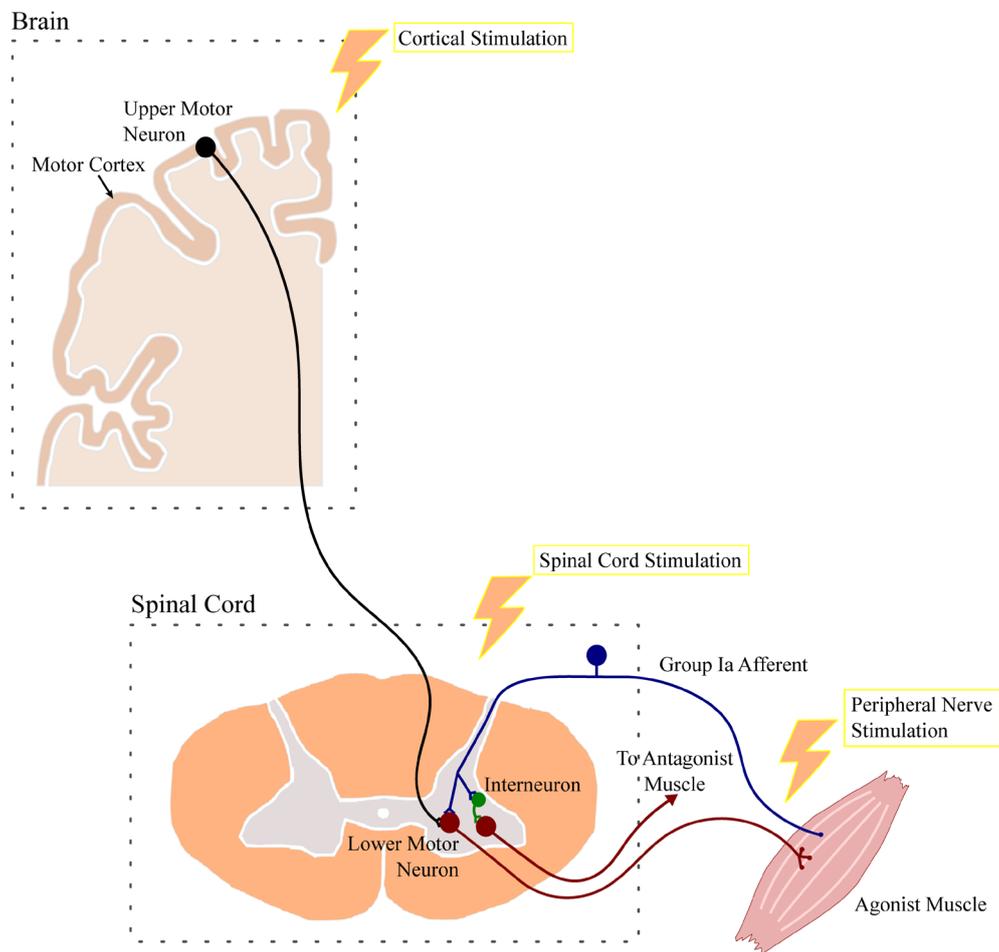


Figure 1-1: A simplified diagram of the motor system for controlling an upper limb muscle

Voluntary commands are sent from the motor cortex (upper motor neuron) to the spinal cord, where they synapse onto intra-spinal circuitry (not shown) and lower motor neurons. The signal is then passed to the muscle, via efferent pathways which exit the spinal cord through the ventral roots, to generate a contraction. Sensory input enters the spinal cord via the dorsal roots, and can be projected up to supraspinal structures, and/or processed within the cord. An afferent input may act upon more than one muscle, for example, it may directly excite the flexor whilst, via an interneuron, inhibiting the extensor. This can bring-about reciprocal inhibition where an agonist and antagonist muscle pair are respectively excited and inhibited by the same afferent input. This is reciprocal inhibition is utilised in stretch reflexes.

1.3.2 Stimulation of the motor system

To manipulate the motor system, stimulation can be applied at the three locations shown in Figure 1-1: (1) the brain, (2) the spinal cord, and (3) the peripheral nerves and muscles. Each

of these locations is associated with different techniques, and accompanying advantages and disadvantages.

In animal models, cortical stimulation is often applied by invasively applying electrical stimulation directly to the neural tissue. This allows precise stimulation of cortical regions. However, electrical stimulation does not discriminate between cell type, which is where new more selective techniques such as optogenetics might offer advantages [40]. While cortical stimulation has been trialled in humans for rehabilitation following stroke [41], non-invasive techniques have clear advantages, with transcranial magnetic stimulation (TMS) prevalent in the field of neural plasticity [42, 43]. TMS uses an electromagnetic coil to apply a rapidly changing magnetic field over the scalp to induce electrical currents in the brain, which if applied over the motor cortex, can generate detectable responses in upper and lower limb muscles [44]. TMS is typically favoured to an alternative technique known as transcranial electrical stimulation (TES) which in addition to the cortex, can stimulate muscles located on the scalp and skin pain receptors, resulting in discomfort [44]. Less specific non-invasive approaches such as transcranial direct current stimulation (tDCS) [45-47], which typically uses two large electrodes placed on the scalp, are also used to modulate cortical activity on a more global scale.

Invasive stimulation of the spinal cord via epidural stimulation, where an electrode is placed on the dorsal surface of the spinal cord, is well established in the field of pain management [48]. However, it is undergoing a resurgence in the field of motor control, particularly for the lower limb and the generation of locomotion [49-51]. It can also be paired with a brain-computer interface (BCI) which may enhance neural plasticity and create an intuitive control system [52, 53]. An alternative approach, intraspinal micro-stimulation, where electrodes penetrate the spinal cord, is also being investigated by several groups [54-56]. In both cases, it is believed that local networks of neurons in the spinal cord are being stimulated. Researchers are now investigating a non-invasive variant known as transcutaneous spinal cord stimulation (tSCS) [57], with reports that both epidural and transcutaneous methodologies can stimulate the same posterior reflex pathways [58]. In particular, recent studies have reported that high frequency tSCS (10kHz) modulated by a lower frequency (e.g. 30Hz) is 'pain free' and can be used to modulate upper and lower limb circuitry [59-61]. Furthermore, it is reported that this technique can improve function in humans following SCI [60-63], although larger studies with control groups and independent, blinded outcome assessors are required to assess the wider implications of this research.

Peripheral nerve stimulation (PNS) is achieved by delivering a train of electrical pulses to the nerve fibre. This is often applied non-invasively by neurophysiologists in nerve conduction studies using a bar electrode, as well as in paired associative stimulation (PAS) studies combined with TMS [43]. As the nerve contains both efferent and afferent fibres, stimulation may affect both pathways, and depending on where along its length it is stimulated, it may innervate several muscles. This is in contrast to spinal cord stimulation (SCS) where the efferent and afferent pathways have separated to enter the ventral and dorsal roots respectively, but muscle selectivity is very limited.

To generate useful movements, a common PNS technique known as functional electrical stimulation (FES) is used [64, 65]. This is the application of small electrical charges to motor nerves just before they enter the muscle via surface or implanted electrodes. An early commercialised assistive FES device used invasively implanted electrodes [66] and although promising results were published [67, 68], it is reported that the company behind the NeuroControl Freehand System stopped marketing the device in 2001 [64]. Implanted technologies are associated with additional challenges such as invasive surgery, the risk of infection, high costs and reduced reversibility of interventions. Nevertheless, implanted FES devices have continued to be developed [69] and one was recently used in the proof of concept BrainGate2 trial [70], which demonstrated that when combined with a BCI, the participant had increased control of upper limb movements whilst using the device.

Non-invasive FES is one of the most common peripheral stimulation techniques used by research groups investigating ‘neurorehabilitation’ [64, 71-76]. In addition to being non-invasive, it offers many advantages over alternative stimulation techniques, such as the availability of commercial devices, the range of muscle groups that can be stimulated, and the relative ease of use. Similar to other PNS techniques, FES may stimulate both efferent and afferent pathways, which might not be desirable for the precise control of neural activity.

Importantly, a recent systematic review with meta-analysis found it to improve upper limb activity after stroke compared to control groups [77]. Also following stroke, it has been reported to reduce spasticity and improve motion [78]. Nevertheless, FES does have a predisposition to cause muscle fatigue through reverse recruitment of muscle fibres [65] and a limited ability to stimulate fine motor movements. Furthermore, despite Howlett et al. concluding that there was evidence that FES had a small to moderate positive effect, including chronic stroke survivors with upper limb impairment, another recent review did not find

evidence of significant improvements to activities of daily living when FES was initiated more than one year after stroke [77, 79]. This inconsistency can be partially explained by the fact that these two reviews did not consider any of the same upper limb studies, showing differences in search criteria. Moreover, small studies often lack sufficient controls, blinding and statistical power to find clinically relevant differences. Indeed, both reviews commented on the lack of available data, and made the case for larger clinical studies. However, for that to occur, the field must agree on a standardised implementation of FES which can be applied in a clinical environment.

Whilst the outcomes of these reviews with meta-analyses should not be dismissed, it is of value to appreciate the levels of recovery being reported by research groups undertaking these smaller studies. Mann et al. delivered FES to extend the elbow and open hand fully without discomfort in stroke survivors [80]. Stimulation was cycled on and off for up to 30 minutes in a fixed pattern rather than paired with a task. Following 12 weeks of treatment, participants (n=11) showed an average improvement of 14.4 points on the Action Research Arm Test (ARAT) [81], furthermore these improvements were maintained at 24 weeks (i.e. 12 weeks after the treatment was stopped). A control group (n=11) which only received self-administered passive stretching also showed improvements (10.1 points), and although also maintained at 24 weeks, these were significantly less. It is of note that the study concluded that it would be beneficial to develop a triggering device to enable the use of stimulation during functional tasks.

So far, we have predominantly considered electrical stimulation, but an alternative solution is a dynamic orthosis, robot or exoskeleton [82]. Here, a mechatronic device passively moves the joint, and these movements can be combined with a task or computer game [83], or paired with inferred voluntary commands, for example, detected using electroencephalography (EEG) [84]. Robot-assisted training can facilitate the delivery of large doses of training, and the completion of repetitive practice is believed to drive Hebbian plasticity [85, 86]. Furthermore, these devices have shown promise [82, 83, 87], with robot assisted upper limb training currently the subject of a large randomised control trial [88]. While these devices will not directly stimulate efferent pathways, they will activate afferent fibres through passive flexion and extension of joints. The cost of these devices is often high and this restricts accessibility [89], but if clinical effectiveness is proven, it is anticipated that economies of scale and competition between manufacturers will lead to substantial reductions in the price.

This wide range of techniques provides researchers with many tools to modulate and control neural activity in the motor system, and in doing so, it may be possible to induce neural repair to drive recovery following a stroke or SCI.

1.3.3 Neural plasticity

‘Neurorehabilitation’ aims to restore function following neurological damage by inducing neural plasticity. This phenomenon, by which connections in the nervous system can be either strengthened or weakened by relative timing of the activity of neurons, was pioneered in the 1940s by Donald Hebb [86] and is often summarised as ‘cells that fire together wire together’ [90], or in his own words:

“When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased” [86]

While the actual processes are more complex, and the temporal order of pre- and post-synaptic firing is important [91], there is a clear opportunity to utilise this property of the nervous system to drive neural repair. Indeed, researchers have demonstrated that this permanent alteration of neuronal connectivity (‘Hebbian’ plasticity) can be driven by a number of different protocols. These were categorised by Jackson and Zimmerman as: repetitive stimulation, paired stimulation and closed-loop stimulation [24], as shown in Figure 1-2.

Repetitive stimulation aims to generate correlated pre- and post-synaptic neuronal activity by repetitive activation of a pathway [24]. This approach was demonstrated in rehabilitative setting by Carmel and colleagues who used a rat model to show that repetitive stimulation of the uninjured motor cortex, following unilateral injury, promoted improvements in skilled locomotion [92]. This supported the idea that repetitive stimulation can be used to drive neural plasticity with functional benefits. However, this protocol, and others like it, require relatively long-periods of training and large numbers of stimuli, which might not be practical in humans. It has subsequently been suggested that paired stimulation of cortical and spinal or peripheral targets may expedite the process [93].

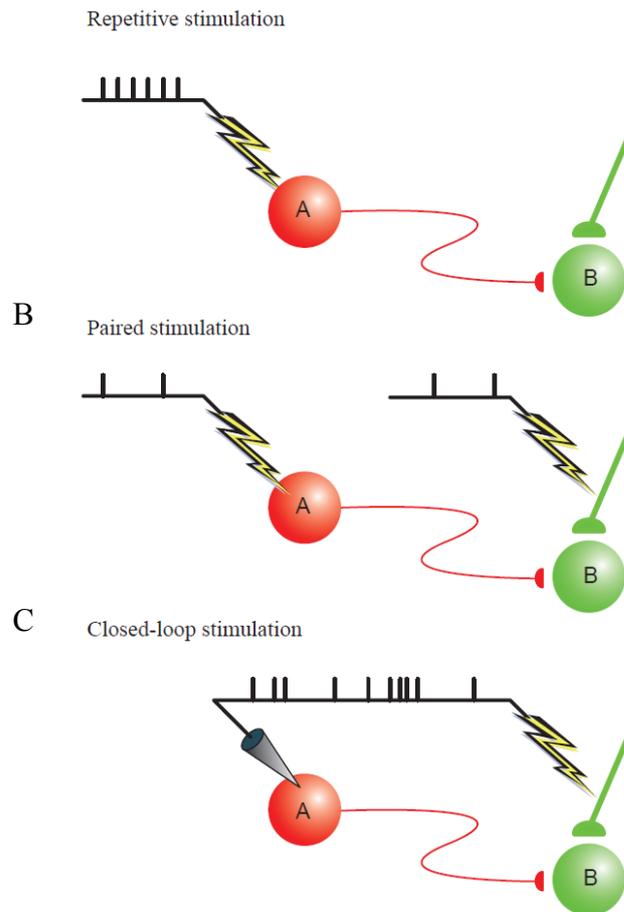


Figure 1-2: Three different protocols for inducing Hebbian plasticity

Three different approaches to inducing plasticity according to Hebbian plasticity. Panel A – Repetitive stimulation, where extrinsic stimuli applied to neuron A, via a single pathway, generate a strong and consistent response in neuron B. Panel B – Paired stimulation of both neuron A and B strengthens the connection between the two neurons. Panel C – Endogenous activity from neuron A is used to trigger stimulation of neuron B using a closed-loop. Reprinted with permission from Springer Nature: Springer Nature, *Nature Reviews Neurology, Neural interfaces for the brain and spinal cord—restoring motor function*, Andrew Jackson & Jonas B. Zimmermann, © Macmillan Publishers Limited (2012), www.nature.com/nrneurol/ [24].

A seminal paper on paired stimulation was published by Stefan et al. [94]. In humans, they paired transcranial magnetic stimulation (TMS) with low frequency peripheral nerve stimulation (PNS) to the median nerve, and recorded increased responses in the abductor pollicis brevis muscle (APB). Further testing suggested that this was caused by plasticity in the motor cortex, driven by associative long term potentiation of either cortical synapses or related neural mechanisms. A similar study was conducted by Song and colleagues, who in a rat model with a pyramidal tract lesion, paired motor cortex stimulation with SCS, and reported cortical spinal tract repair and motor recovery [93]. They noted that the pairing of cortical and spinal stimulation, led to recovery in much shorter time-frames than repetitive stimulation of a single site.

‘Open-loop’ protocols such as these, do not use feedback to control stimulation, which makes integration into natural tasks challenging. Furthermore, protocols such that presented by Stefan et al. require specialist equipment and skilled operators to deliver stimulation [94]. An alternative approach is ‘closed-loop’ stimulation, and one of the first demonstrations was by Jackson et al. [95]. They artificially created a connection between two areas of motor cortex by using activity recorded from one area to trigger electrical stimulation in the other. This utilised the natural firing of the brain, and could be operated with minimal input over a prolonged period of time. They showed that this closed-loop set-up could strengthen connections between the two areas, and that the effect persisted following the end of the intervention. The technique was developed further by Nishimura et al. who paired cortical recordings with intraspinal micro-stimulation, and demonstrated that the strength of connections between the motor cortex and spinal cord could be strengthened or weakened depending on the relative timing of the recorded activity and the stimulation [96].

Since these pioneering studies, a closed-loop system has been shown to have a positive rehabilitative effect in a rat model of SCI [23]. Here, intraspinal micro-stimulation below the site of injury was synchronised with the arrival volitional motor commands from the motor cortex, signalled by muscle activity in the impaired forelimb. This intervention was found to improve function on a forelimb reach and grasp task, and further demonstrated the potential of closed-loop systems to drive neural plasticity for rehabilitation. However, the translation of therapies from animal model to humans is challenging, and as such, these studies must be interpreted with care [28].

The scientific and engineering challenge for researchers developing closed-loop devices is two-fold: firstly, the inference of brain activity or motor intent, and secondly, the delivery of appropriately timed stimulation. Closed-loop devices have the benefit that the peripheral stimulation, such as FES, can also be used to aid the completion of functional tasks in an intuitive manner, which will likely aid the translation into humans.

Two potential solutions were reported by McGie and colleagues who combined FES with electroencephalography (EEG), and separately, with non-invasive electromyography (EMG) to demonstrate short-term changes in neural plasticity following a short intervention [74]. Electroencephalography (EEG) involves placing an array of non-invasive electrodes on the scalp and recording electrical signals to infer underlying brain activity, while EMG is used to record activity from the muscle and can therefore be used to detect attempted movements. The

group noted that to induce plasticity, it was critical that FES was applied when the participant voluntarily tried to move their hand.

Whether these short-term changes in neural plasticity would translate into functional improvements was unknown, but the methodology has now been supported by a recent study that combined EEG with FES in chronic stroke survivors [97]. This study reported lasting improvements 6-12 months following the end of a six week therapy period (10 sessions, 60 minutes each), and found increases in functional connectivity between motor areas in the affected hemisphere [97]. The researchers cited the contingent activity of natural efferent and afferent pathways as being crucial for plasticity. However, the intervention was compared to a sham-FES group, and to be clinically relevant, a larger sample size and comparisons with a conventional therapy, as well as FES delivered passively or via a cheaper control system, such as a button press, would be beneficial. Nevertheless, this is a promising result, and further support for closed-loop devices came from a meta-analysis by Bolton et al. [98]. They found evidence for the use of EMG-triggered neuromuscular stimulation (i.e. FES) as an effective post-stroke intervention.

An alternative closed-loop approach is to infer cortical activity using real-time kinematic measures. For example, Meadmore et al. used an iterative learning algorithm based on movement kinematics to apply FES to the shoulder, elbow and wrist [75]. A pilot study of 5 participants with hemiplegia suggested that this system may reduce upper limb impairments following stroke. Additional work will be required to validate this small study, but the result supports the principle of combining voluntary motor intent with peripheral stimulation.

Complex systems such as those reported above can be a challenge to evaluate due to: a limited range of movements; a need for engineering support; cost; and the requirement to be located in a specialist lab. Therefore, regardless of efficacy and effectiveness, for an intervention to have wider impact and to facilitate the high dosages reported to be crucial for rehabilitation, it must be more akin to home-based exercise equipment than something found in neuroscience laboratory. The recently reported FES-UPP project sought to address these concerns by developing a flexible kinematic based system designed for use by therapists with little to no engineering support or previous FES experience [73]. While this promising system could be used to deliver high intensity therapy, functional benefits and the cost were not reported.

So far, the closed-loop solutions discussed have typically utilised FES. It is an established and accessible method of stimulating the nervous system in a closed-loop set-up, but in search of

novel solutions it is important that other technologies such as robotics [83], dynamic orthoses [82] and transcutaneous spinal cord stimulation [57, 61] are also considered.

1.3.4 Neurological conditions

A wide range of neurological conditions may lead to upper limb impairment. These include multiple sclerosis, motor neurone disease, Parkinson's disease (PD), traumatic head injury, as well as stroke and SCI. When choosing which conditions to target with a novel intervention, it was important that they were conditions that would be likely to respond to neural plasticity driven by concurrent activity in the cortex and peripheral or spinal nerves. For example, PD is caused by a loss of dopaminergic neurons in the brain region known as the substantia nigra [99], and there is no strong scientific basis for believing that paired stimulation delivered in the manner discussed would be beneficial. Instead, PD is targeted by other stimulation techniques, such as deep brain stimulation [99].

Although stroke principally effects upper motor neurons and supraspinal pathways, and SCI results in damage to upper and lower motor neurons and spinal pathways, it was reasonable to believe that both conditions would benefit from an intervention that facilitates or strengthens weakened pathways between the cortex and the periphery. Stimulation techniques such as FES require the nerve fibre between the spinal cord and muscle to be intact, and this is the case for stroke, and often for SCI. FES is also used by people with multiple sclerosis, and they may also benefit from a paired stimulation intervention, although this was not investigated in this thesis.

Newcastle University has expertise on the evaluation of rehabilitative stroke care, and a strong collaboration the Miami Project to Cure Paralysis (University of Miami) which has a focus on SCI. These two groups provided an excellent knowledge base and access to participants with stroke and SCI, which coupled with the global demand for novel rehabilitative solutions for these conditions, made them an obvious focus for the intervention developed in this thesis.

1.4 This thesis

There is a clear demand for the development of new therapies for upper limb rehabilitation following stroke and SCI. Traditional approaches to rehabilitation have limited benefit, but research has shown that driving neural plasticity using a closed-loop system may provide opportunities to innovate in this field. However, new therapies must demonstrate more than efficacy; they must be adaptable, user-focused and cost effective.

This thesis describes the development of a novel closed-loop device, which in addition to seeking to exploit neural plasticity, allows a user to complete many repetitions of a functional task, with minimal support from another person. The device is designed to be low cost and suitable for use in the home or clinic. Furthermore, the system offers the flexibility to optimise the intervention by adjusting the relative timings of inferred activity and stimulation. In the first instance the system utilises FES, but tSCS is also investigated.

In this chapter, I have given an overview of the state-of-play with regards to upper rehabilitation and emerging efforts to use Hebbian plasticity to drive neurorehabilitation. In Chapter 2, I describe the development of a novel device and intervention, and in Chapter 3 I report the findings of a study with participants with SCI. In Chapter 4, I present a series of studies with stroke survivors, and in Chapter 5, I seek to understand the mechanisms by which the intervention may be acting and how it could be optimised in healthy able-bodied volunteers. In Chapter 6, I investigate tSCS as an alternative to, or as a complementary stimulation technique for, FES. Finally, Chapter 7 brings this thesis to a close with a general discussion.

Chapter 2

Development of a closed-loop device for rehabilitation following stroke and SCI

Aim:

- To develop a device that seeks to exploit neuroplasticity for the rehabilitation of the upper limb following neurological conditions such as stroke and spinal cord injury (SCI).

Objectives:

- Explore the different options for inferring motor intent and stimulating the nervous system to drive neural plasticity for recovery of voluntary upper limb movement
 - Design, build and test prototype devices, and collect feedback from user groups
 - Select a final concept to take forward for further testing with participants with stroke and SCI.
-

Acknowledgements / contributions: Many thanks to Norman Charlton and Joe Wardle who took my initial concept and sketches and used their knowledge and expertise to create the final mechanical design and build presented in this chapter. Further thanks to Felipe De Carvalho for his invaluable support and input on the electrical design of the device, and Paul Taylor (Odstock Medical Ltd.) for his expertise and advice on FES stimulators. The design of the device was greatly forwarded by input from Stuart Baker and Anna Basu. Additional thanks to Sarah Moore and Helen Bosomworth for their expertise and advice, and Jane Burridge for her insights on the pulley design.

I was responsible for the design, build and testing of the final device and prototypes, with significant input from the aforementioned people. Andrew Jackson proposed the original concept of using a dataglove to predict the movement of the unaffected limb, and contributed throughout the design process, especially with regards to approaches for inducing neuroplasticity. Helen Rodgers offered guidance and critical feedback from a clinical perspective, in particular by directing my attention towards the findings of the 2014 Cochrane Review ('Interventions for improving upper limb function after stroke') [11]. I collected feedback from a user group at Institute of Neurosciences, Kolkata (I-NK), and this was supported by Stuart Baker, Ravi Singh, Supriyo Choudhury, Hrishikesh Kumar and Robin Sengupta, as well as Isabel Glover who collected additional feedback at I-NK. My visits and presentations to the North East Stroke Patient & Carers Group were facilitated by Chris Price, and many thanks to the members of this group, and other support groups I attended, for their kind hospitality and useful input. Finally, many thanks to all the volunteers, the physiotherapist focus group and everyone who contributed to the study.

Sections of this chapter were previously reported in Hodkin et al. [1] © 2018 IEEE.

2.1 Introduction

There is a need for novel interventions to be incorporated into rehabilitation programmes to improve upper limb recovery following neurological conditions such as stroke and spinal cord injury (SCI). In the previous chapter, it was suggested that an approach that combined a high number of task repetitions, limb mobilisation and appropriately timed electrical stimulation delivered in a closed-loop, could potentially drive neural plasticity, leading to positive rehabilitative outcomes. In this chapter, we explore a number of possible solutions and describe a novel device developed for further investigation.

A closed-loop device requires two key components. Firstly, a method of sensing the users motor intent (voluntary brain activity), and secondly, a system to provide stimulation paired with that intent. As described in the previous chapter, devices have previously been developed in this field, but as of yet, clinical effectiveness has not been widely established. Therefore, prior to starting the design process, it was important to define an acceptance criteria that would address factors that might have contributed to this limited translation from bench-to-bedside.

Acceptance criteria:

1. Suitable for home and clinical use
2. User friendly
3. Robust and reliable
4. Low-cost
5. Only limited input required by a therapist or carer
6. Adaptability to support a range of impairments
7. Does not require significant on-going support or specialist engineering knowledge
8. Versatile for testing different plasticity protocols
9. Testable in a large clinical trial, with limited engineering support.

2.2 Design considerations

2.2.1 Stimulation of peripheral nerves and the spinal cord

A challenge of working with people with upper limb impairment is that movements may be restricted by paralysis, spasticity and muscle hypertonia. Therefore, in a closed-loop system designed to drive neural plasticity, it is advantageous for the stimulation to fulfil two functions:

(1) to enable completion of a movement, and (2) to provide a peripheral stimulus to be paired with motor intent.

This can be achieved by functional electrical stimulation (FES), which can induce functional muscular contractions, enabling participants to overcome immobilisation and complete a movement [65]. Therefore, non-invasive FES is an obvious choice for the design of a new system, although as discussed in the previous chapter, it has disadvantages such as reverse recruitment of muscle fibres [65], a limited ability to stimulate fine motor movements and some questions over its efficacy in chronic stroke [79].

Implanted FES technology is associated with greater costs and complexity, and therefore falls outside the acceptance criteria. Similarly, the risks of invasive surgery, cost, the need for specialist installation, and limited evidence of clinical effectiveness for upper limb rehabilitation, mean that cortical and epidural spinal stimulation remain inaccessible for the majority of the population. An alternative solution is to use a dynamic orthosis or robotic device. However, suitable robotics are not widely available and the cost can be high [89]. Furthermore, orthoses face many challenges with regards to the diverse range of impairments caused by stroke and SCI, and the time and cost associated with developing devices.

Transcutaneous spinal cord stimulation (tSCS) may offer an alternative to FES, and following further development, it could meet the acceptance criteria for this project [57-60, 100, 101]. Therefore, the preliminary work in this thesis will make use of non-invasive FES (Chapters 2 to 5), but tSCS will also be investigated (Chapter 6) to understand how it might be later incorporated into the intervention, either in addition to, or as a substitute for, FES.

2.2.2 Methods of inferring motor intent

Direct recordings from neurons in the motor cortex and posterior parietal cortex have been used in non-human primates to predict movement intent [95, 96, 102], and the first steps are now being made to replicate this work in humans [70, 103, 104]. However, these devices are still far from being available in normal clinical practice, and for the purposes of this study, less invasive alternatives were considered.

Electroencephalography (EEG) has been used in closed-loop systems combined with both FES and an orthosis [71, 84, 97, 105], but the set-up time, cost and complexity of such systems limits the wider accessibility of them. Electromyography (EMG) is used to record muscle activity to subsequently infer voluntary commands [72, 106, 107], with some devices even

being commercialised [107]. However, EMG systems require a certain level of residual function that may not be present in a paralysed limb, and the initiation of voluntary commands can lead to co-contractions that resist the intended movement [73].

While FES devices for upper limb rehabilitation are not well-established in a clinical setting, lessons may be learned from lower-limb rehabilitation where FES systems are commonly used for assistive devices for foot drop [108]. Numerous commercial devices are available (see WalkAide (Innovative Neurotronics Inc.), NESS L300 (Bioness Inc.), ODFS Pace (Odstock Medical Ltd.)) and typically, they do not use complex physiological measures, but kinematic signals associated with walking. This allows stimulation to be combined with voluntary intent, and a high number of repetitions to be completed. Despite there being no direct correlate of walking in the upper limb in humans, a cyclical task has obvious advantages with regards to automation and completing a high number of repetitions.

Kinematic systems that measure acceleration, joint angle or use motion capture, have been used by upper limb research groups, allowing inferences about voluntary brain activity to be made [73, 75, 76, 109]. While these systems vary in cost, flexibility and complexity, a key limitation is that to be detected, movements need to be made. So while FES might enable the person to complete an action, if they cannot initiate that movement, the brain activity cannot be inferred.

The systems discussed above infer endogenous brain activity by recording a surrogate marker of that activity, i.e. electric fields on the scalp, muscle activity or limb movements, and typically use this marker to deliver appropriately timed assistive stimulation (e.g. FES). In theory, this allows the participant to complete a self-initiated task intuitively. If the requirement to be self-initiated is removed, then an alternative approach whereby FES is purely used as a neurorehabilitative training aid that operates within a pre-defined protocol, rather than as an assistive device, presents new opportunities.

One such opportunity is to stimulate brain using auditory and visual cues, and then infer that it has responded in a predicted manner. For example, if a command is given to a trained human to reach for an object, it is known that they will try to complete this action, even if motor impairment restricts their ability to do so. Furthermore, a reach and grasp movement is a stereotyped movement with clearly defined components: (1) transporting the hand to the object, (2) the formation of the hand to grasp the object and (3) grasping the object [110]. Therefore, once a cue has been given, the brain activity can be inferred and appropriate stimulation provided. This offers a simple, yet reliable method of inferring endogenous brain activity,

which is not contingent on any physiological measure, and resolves the issue with kinematic measures. Movement (reaching and hand opening) can be initiated using a cue or command supported by electrical stimulation (or an orthosis), and once in motion, the resulting brain activity can be inferred using kinematics, and parameters adjusted for completion of the action (grasping).

2.3 Prototypes

The following prototype designs were developed to meet the design considerations discussed in Sections 2.1 and 2.2. In the first instance, an upper limb alternative to a walking motion was sought, and movements were measured in real-time using kinematics. The design then evolved towards uni-manual tasks that were better suited to training activities of daily living, with this being achieved in the final design by utilising cues and more robust kinematics measures.

2.3.1 Vertical pulley

We first considered the repetitive, bi-manual rope pulley task as shown in Figure 2-1. It had the advantage that the participants' hand motions were approximately out-of-phase, and therefore, the position of one hand could be inferred from the position of the other. In the case of stroke, this had the practical significance that the intended motion of the affected hand could be inferred from the movement of the less affected hand, allowing closed-loop control of FES or a hand orthosis.

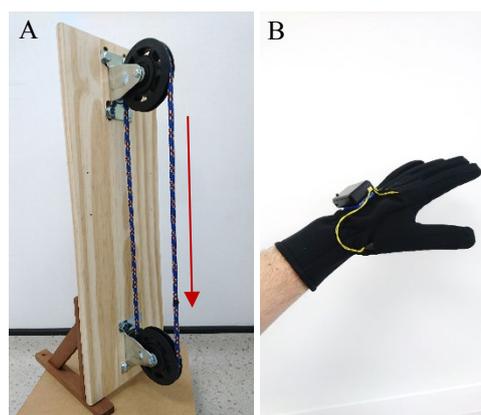


Figure 2-1: A prototype bimanual closed-loop task

Panel A – The vertical pulley. The participant was asked to continuously pull the rope downwards using a hand-over-hand technique. Panel B - A dataglove with an inertial measurement unit (IMU) worn on one hand to record kinematic signals; accelerometry and/or grip aperture. These signals were subsequently processed to provide appropriately timed stimulation to open and close the other hand.

A number of methods were trialled for capturing the kinematics of the less affected hand. These included using a dataglove (VMG 8, Virtual Motion Labs) to record grip aperture and

accelerometry, and separately, a wireless inertial measurement unit (IMU) (Shimmer3 IMU, Shimmer Sensing) to record acceleration. Data were streamed in real-time to a PC running MATLAB (MathWorks Inc.) which controlled an FES stimulator (OS2CHS, Odstock Medical Ltd.) via a custom trigger with a Bluetooth connection. Prototypes showed that this approach was feasible in healthy able-bodied controls, but it was clear following consultation with clinicians that the range-of-motion motion required in the arm and hand would severely limit the number of users, and it would not be suitable for bilateral injuries such as SCI.

2.3.2 Two-sided Pulley

In light of the feedback received regarding the vertical pulley, it was realised that if the need to grasp the pulley was removed, then this would create an alternative solution for training of proximal arm muscles with FES assistance. This resulted in the two-sided pulley shown in Figure 2-2.

Here, the position of one arm was recorded using an IMU (accelerometry), and appropriately timed FES provided to the other arm, facilitated lifting the arm and extension at the elbow. The device was placed in either a horizontal or vertical position, and could also be used without any stimulation, although this fell outside the scope of this thesis.



Figure 2-2: A two-sided pulley for a closed-loop FES task

A wireless IMU was used to capture real-time accelerometry from one arm, and this signal was used to predict the location of the other arm in the movement. FES was subsequently provided to facilitate lifting the arm and extension of the elbow during appropriate phases of the cycle. The device is shown in the vertical position, but could also be used in a horizontal position.

As previously described, data from the IMU (Shimmer3 IMU, Shimmer Sensing) were streamed in real-time to a PC running MATLAB (MathWorks Inc.) that controlled an FES stimulator (OS2CHS, Odstock Medical Ltd.) via a custom trigger with a Bluetooth connection.

The prototype worked well in healthy able-bodied controls, but had several disadvantages. Firstly, it only facilitated a limited range of training, and secondly, if a participant had a weak grip, they would require their hand(s) to be attached to the grip(s). Furthermore, the 2014 Cochrane Review (‘Cochrane overview: Interventions for improving upper function after stroke’) stated that unilateral tasks were preferable to bilateral tasks [11], and while this referred to bilateral tasks where both sides were completing the same motion, and here they were out-of-phase, it was not clear how this would impact rehabilitative outcomes with this device.

2.3.3 Uni-manual task

We developed the following task (Figure 2-3) to facilitate uni-manual training without the need for assistance by the other limb. This was particularly important for SCI, where both limbs may be severely affected. An IMU (Shimmer3 IMU, Shimmer Sensing) was placed on the wrist to measure acceleration and wrist angle, and the participant was asked to pick up a series of blocks and placed them on a raised platform with the block rotated 90 degrees. The intervention exploited the fact that for this specific task, the signals from the gyroscope and accelerometer were 90 degrees out of phase (see Figure 3-2), and thus the position of the hand relative to the task was known throughout. Stimulation was then automatically applied to facilitate the opening and closing the hand at the appropriate points in the task, allowing the user to pick-up and release the block.

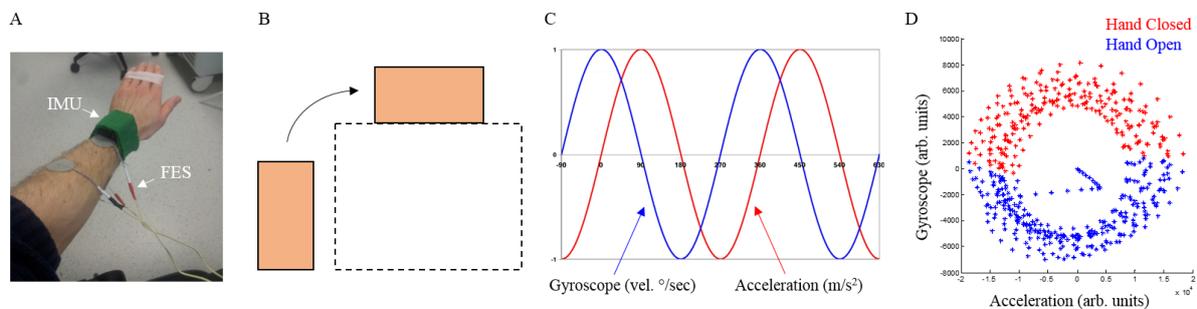


Figure 2-3: A uni-manual block moving task

Panel A – An IMU was attached the wrist, and FES set-up to stimulate the hand, wrist and fingers extensors and flexors. The fingers were ‘buddied’ to improved hand closing with FES. Panel B – A block was lifted, rotated 90° and placed at an elevated height. There were multiple blocks to allow many repetitions of the task, and these could be designed to make rotation of the block intuitive (i.e. appropriately shaped slots at the start and finish positions). Panel C – Signals captured by the IMU (acceleration and angular velocity) were 90° out of phase. Panel D – These signals were processed in real-time (MATLAB, The MathWorks Inc.) allowing the position of the participant in the task to be tracked and FES (OS2CHS, Odstock Medical Ltd.) provided to either open or close the hand at the appropriate time.

The task was demonstrated to work well for healthy able-bodied volunteers in a laboratory setting, but it required reliable and consistent movements, in particular wrist rotation, which may not be present individuals with motor impairment.

2.4 The final device

2.4.1 Rationale

It was evident from the uni-manual task described above, that while movements could be predicted within specified block moving task, further task constraints would be required to provide the robust solution required for upper limb rehabilitation following stroke and SCI. In the task shown in Figure 2-4 the block has been retained, but it has been fixed to a slide rail to prevent accidental or incorrect movements that might otherwise disrupt the participant's progress through the task. Furthermore, the IMU has been replaced by cue (auditory and visual) to drive cortical activity and initiate movements, and proximity sensors to detect the completion of self-paced motions.

As described for the prototypes, non-invasive FES was selected to provide peripheral stimulation, due to its accessibility, ease of use, ability to stimulate both proximal and distal muscles, and the availability of stimulators. This was paired with a control system that was designed to allow the adjustment of the relative timing of cues and stimulation onset, for later investigation of optimal timings for neural plasticity.

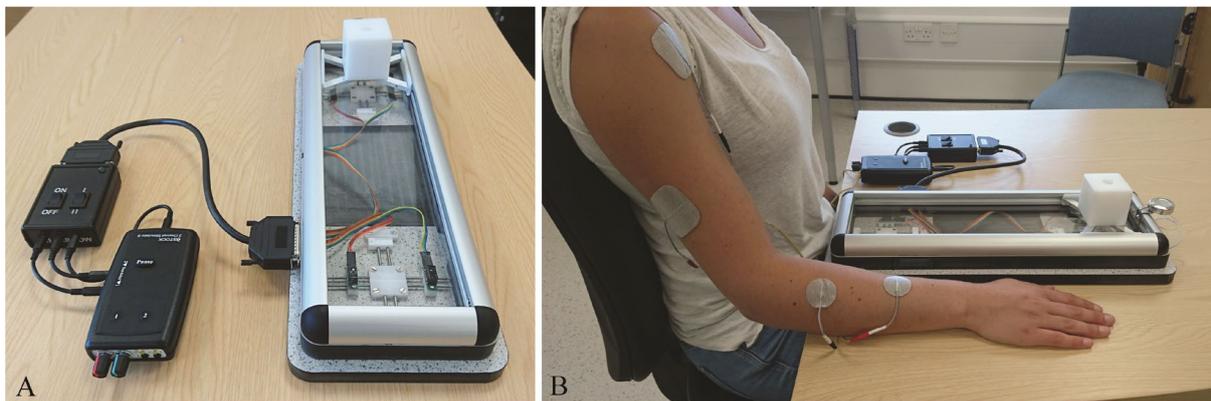


Figure 2-4: The device developed for this thesis

Panel A – Participants reached for a cube and pulled it towards themselves, a distance of 300mm. Assistive stimulation was delivered by an FES stimulator, modified to be controlled by a microcontroller which received input from digital proximity sensors at either end of the rail. Panel B - To stimulate wrist and finger extension the active electrode (cathode) was positioned over extensor digitorum communis (EDC), and the indifferent electrode (anode) over extensor pollicis longus (EPL) and abductor pollicis longus (AbPL). To stimulate extension of the arm, the active electrode was placed over the anterior deltoid and the indifferent electrode over the triceps. The slide rail base was ~460mm x ~165mm. © 2018 IEEE [1].

2.4.2 Description of the device

The device comprised of a custom-made slide rail, with integrated sensors and a real-time link to a FES stimulator via a microcontroller (Figure 2-4, Figure 2-5). The device was placed on a flat surface in front of the participant, with the block at the far end of the rail. This was typically orthogonal to the table edge, but if necessary it was angled to aid reaching. A 50mm cube (60g) was fastened to the rail and tethered by a spring-loaded reel (max force approximately 2N) such that when displaced from start position and released, it automatically returned to the start position, ready for the next movement repetition. This allowed multiple cycles of the reaching and grasping task to be completed automatically.

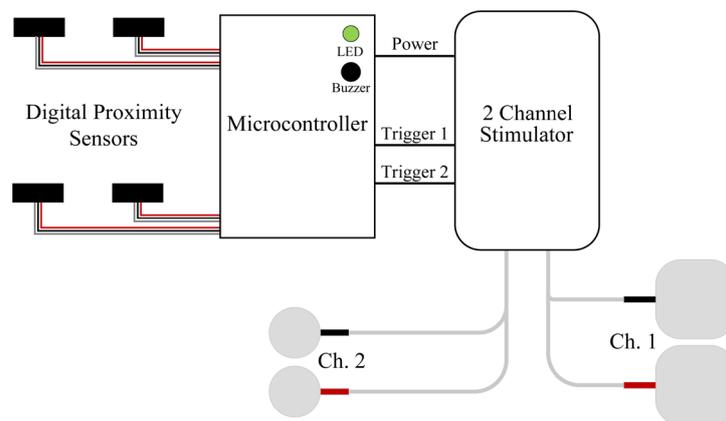


Figure 2-5: A system schematic for the device

A microcontroller generated cues and received inputs from two sets of proximity sensors. It subsequently triggered stimulation to open the hand and extend the arm at appropriate times during the task. © 2018 IEEE [1].

FES was delivered by a 2-channel stimulator (OS2CHS, Odstock Medical Ltd) to open the hand and, for some participants, to extend the arm at the elbow. The trigger was modified to be controlled in real-time by a microcontroller (Arduino Micro) and digital proximity sensors with a 10cm range (GP2Y0D810Z0F, Sharp) at either end of the rail (see Figure 2-5). Auditory and visual cues (a short single (100ms) or double tone (2x100ms) and LED illumination) were used to control task timing. Together with the proximity sensors, this allowed the participant's progress through each trial to be tracked so that stimulation of muscles could be delivered at the appropriate time, creating the closed-loop shown in Figure 2-6.

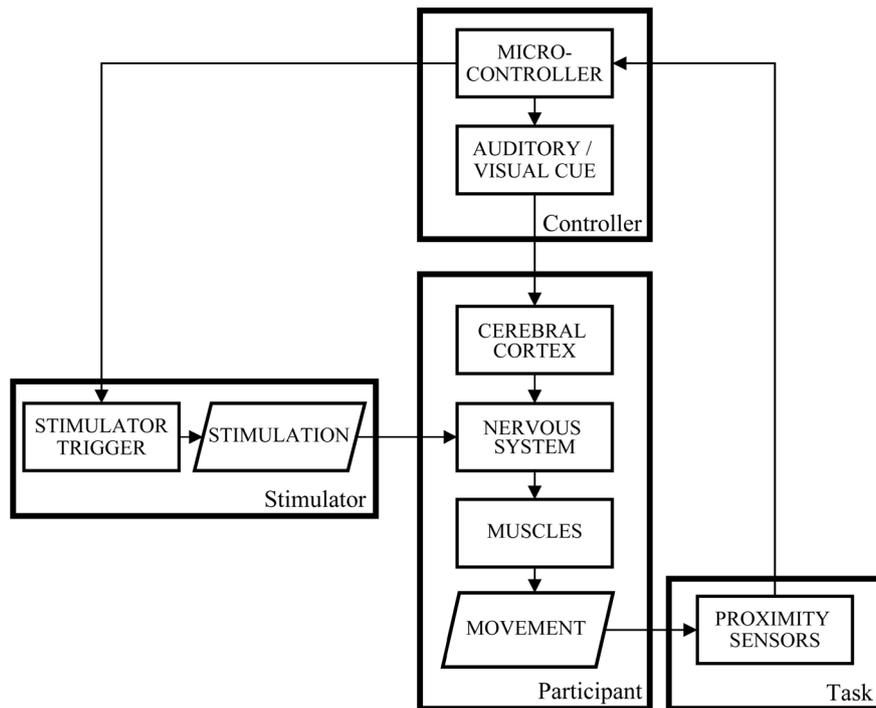


Figure 2-6: The closed-loop created by the device, stimulator, controller and participant
 © 2018 IEEE [1].

At the start of each trial, auditory and visual cues indicated that the participant should reach towards and grasp the block. At the same time, stimulation was delivered to enhance this movement, e.g. stimulating the hand to open and the arm to extend. The end of the reaching phase was determined using a proximity sensor at the far-end of the slide to detect in real-time when hand was over the block. Thus stimulation was delivered through the whole outwards movement, irrespective of the movement duration. Once the block had been reached, stimulation was automatically turned off and participants pulled the block without assistance to the finish position. Again, proximity sensors were used to determine when the block had reached the finish position. Following a 1.5s delay, the participant received a further auditory and visual cue to release the block, and this releasing movement was assisted by concurrent stimulation to open the hand. Once released, the block returned automatically to the start position, triggering the end of stimulation. The next trial began after a rest period of 5 seconds.

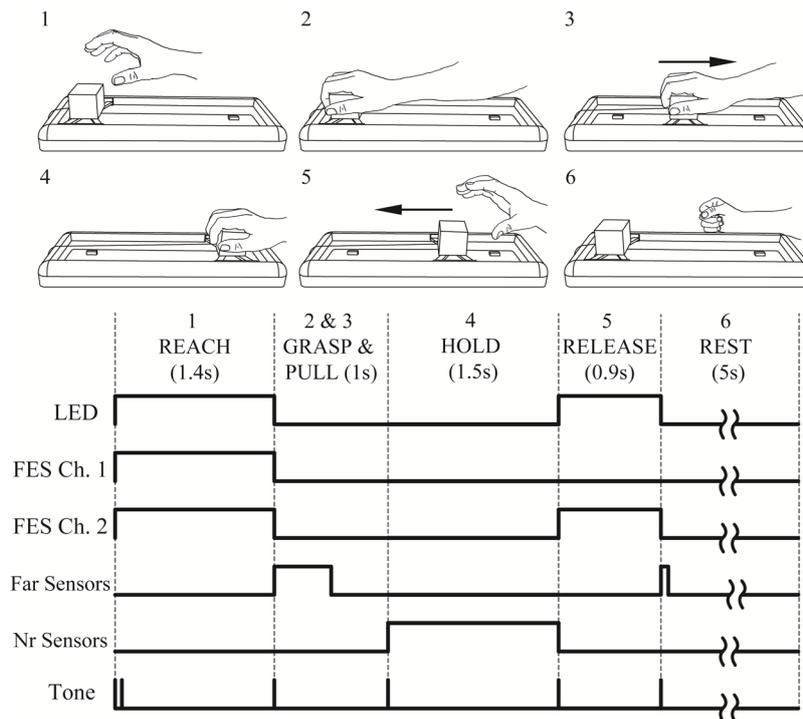


Figure 2-7: The intervention protocol

1. The participant was given an auditory (double tone) and visual cue (LED on) to reach and grasp the 5cm cube, and FES was given to open the hand and, in most cases, extend the arm. 2. When proximity sensors (10cm range) detected that the open hand was over the block (marked by a single tone, LED off), the FES was turned off allowing the block to be gripped. 3. The participant pulled the block to the finish position with no FES assistance. 4. A proximity sensor detected the return was complete (single tone) and the microcontroller initiated a 1.5s delay. 5. Cues (single tone, LED on) indicated that the block should be released and FES was applied to open the hand. 6. When proximity sensors detected that the release was complete (the block was in the start position), FES was turned off (single tone, LED off). The participant then rested for 5 seconds before returning to step 1. Timings shown were calculated using data from participants with SCI ($n=7$) for a block of 25 trials on day 3 of the intervention (see Chapter 3). Timings (mean (\pm SE)) are: Reach 1.4s (\pm 0.2), Grasp and Pull 1.0s (\pm 0.15), Hold 1.5s, Release 0.9s (\pm 0.07), and Rest 5s. Similar timings were observed for participants with stroke (see Chapter 4). © 2018 IEEE [1].

The combination of cued movement initiation and automated detection of movement completion allowed stimulation to be reliably delivered contingent on the timing of the self-paced task epochs (e.g. reaching outwards and back) whilst maintaining a steady rate of progress through multiple trials. The protocol with further details of cues and timings is illustrated in Figure 2-7. Note that typically the stimulation and cues were delivered at the same time, but the system had the capacity for these timings to be adjusted, and the potential impact on neural plasticity is explored in Chapter 5.

2.5 User group feedback

2.5.1 Stroke survivor user group

2.5.1.1 *Introduction / Methods*

In July 2016, the device was demonstrated to the North East Stroke Patient & Carers Group. The device received a generally positive reception, and one attendee demonstrated completing the reach & grasp task without stimulation. A subsequent session was arranged at the Institute of Neurosciences, Kolkata (I-NK), to invite volunteers to try the device for a short-period, i.e. 10 to 25 repetitions of the task. Ethical approval was given by the local ethics committee, and volunteers were pre-screened so that those attending were already believed to have a level of upper limb weakness compatible with using the device, i.e. some residual movement, but restricted ability to complete a reaching and grasping task. FES was only applied to open the hand, and not to extend the arm at the elbow.

2.5.1.2 *Results*

The demonstrator recorded observations for 11 participants (mean \pm SE age 46 \pm 4, years since first stroke 2 \pm 0.6), and reported a positive experience for 10 out of the 11 participants. One out of the 11 gave mixed feedback, as although the extension did help to open his hand, there was an unsatisfactory amount of ‘clawing’ of the fingers. Hand and finger extension was not always complete in the other participants, but it was sufficient to aid completion of the task. A support arm and splint were used to assist one participant in completing the task. Scores on a commonly used functional assessment, the Action Research Arm Test (ARAT) [81, 111], were available for 9 out of the 11 participants. The average score was (mean \pm SE) 15 \pm 5, which is relevant to a discussion on the applicability of the device to a broader population in Chapter 4.

2.5.1.3 *Further findings*

In general, the task was well received, but the first prototype of the device only used an auditory cue. It was found that in a noisy environment, or if the participant suffered from deafness, this presented a challenge, and participants sometimes compensated by using the stimulation as a cue. The visual cue described in the previous section (LED illumination) was subsequently added to the device to resolve this issue.

Participants sometimes found the task a little confusing, and an initial training period was required (5 to 10 minutes) to learn the task and adjust the sensors to ensure correct timing of stimulation. It was apparent that a splint or arm support may be beneficial for participants with

weak proximal muscles, as they struggled to achieve the elevation and distance required to reach the block at the start of the task. Furthermore, four participants used the device in a horizontal position (sliding from side-to-side) as they did not have a sufficient range of motion to reach the full distance. Consequently, it was decided that it would be beneficial for the blocks start position to be adjustable, thus allowing the vertical distance reached to be reduced. This was integrated into a later iteration of the device by placing the far sensors on a sliding plate and including adjustable end-stops on the slide-rail. The sliding plate can be seen in the device shown in Figure 2-4.

2.5.2 Physiotherapist focus group

2.5.2.1 Methods

A questionnaire comprising of predominately structured questions (Likert scale) was composed to gather feedback on the device from a focus group of physiotherapists. Prior to completing the questionnaire, a presentation on the device, with a short demonstration, was given. The questionnaire also provided the opportunity to make additional freehand comments.

2.5.2.2 Results

Nine physiotherapists with a range of experience from the National Health Service (NHS) in the North East of England attended the focus group. Seven agreed that the task and choice of muscles stimulated would be appropriate for a substantial proportion of stroke survivors they worked with, and if appropriate, eight said that they would be happy to use the system. None of these therapists currently used FES more than ‘every once in a while’, with cost and availability of devices reported as barriers to use.

Physiotherapist Focus Group (n=9)

Regarding the reach and grasp device presented today:

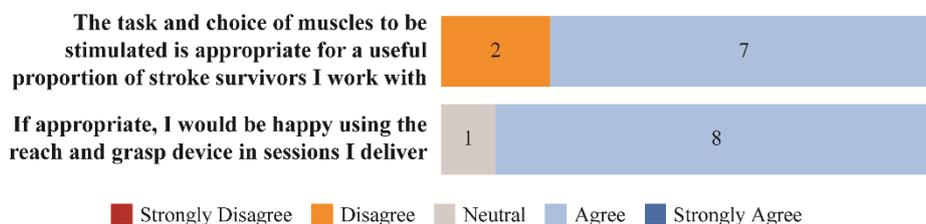


Figure 2-8: A selection of the qualitative data collected from the physiotherapist focus group © 2018 IEEE [1].

2.5.2.3 Discussion

Feedback from this focus group demonstrated that if shown to be effective, the device was likely to receive a positive reception from physiotherapists.

2.6 Future designs

It is important to note that with regards to choice of task, muscles to be trained and difficulty level, this device does not allow the same level of variability as a physiotherapist led session. There was a trade-off between the low-cost, simple interface and high repetitions provided by using the device, and the personalized care provided by a therapist. However, the device does have in-built adaptability; the 5cm cube can easily be swapped for an object of a different size, texture and / or shape, and the sensor positions can be adjusted accordingly. The distance reached can also be reduced, and there is the potential to upgrade the spring-loaded reel to include adjustable resistance. Stimulation parameters can be set to match the user's needs, and the electrode positions adjusted to target specific muscles.

Adaptability for a range of impairments was an important design criteria, and while the device described above does offer versatility, it is also conceivable that further devices based on similar principles of cueing and sensing of limb position could be developed for participants with higher or lower levels of upper limb function.

To illustrate this, Figure 2-9 shows two devices combined in a modular fashion to replicate the prototype pulley devices described earlier. Here, for stroke survivors, the less affected arm can be used to assist the affected side, or both sides can be trained by participants with a bilateral injury such SCI. FES would be applied to assist arm extension, and the blocks could be replaced with grips. The simple toothed pulley system added to the device to facilitate this additional functionality, would be designed to be easily removed when not required. While this device was not tested in this thesis, it demonstrates a possible future iteration of the design.

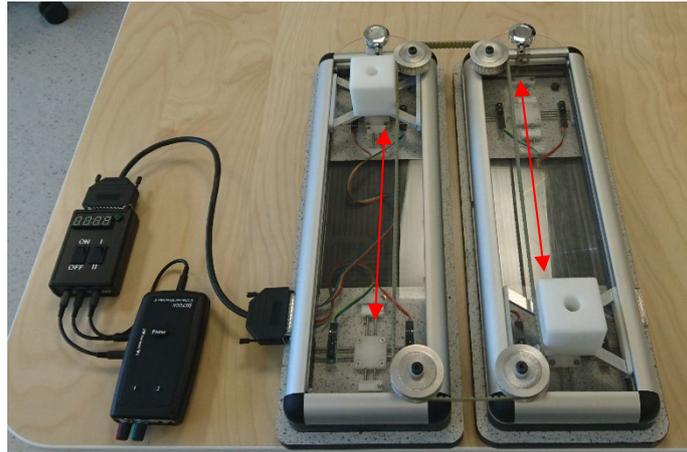


Figure 2-9: Two devices combined in a modular fashion to create a pulley system

This prototype device enables out-of-phase bilateral training, during which stimulation is applied to facilitate arm extension. Furthermore, following stroke, movement of the affected arm can be assisted by the less affected arm. The devices are prevented from slipping using a non-slip mat (not shown).

Chapter 3

Investigations into the utility of the device for upper limb rehabilitation following spinal cord injury

Aim:

- To investigate the utility of the novel device for upper limb rehabilitation following spinal cord injury (SCI).

Objectives:

- Obtain qualitative feedback from participants with SCI on the usability of the device, suitability of the task, and any perceived benefits from a short intervention
 - Use quantitative measures to assess changes in function following a short intervention using the device.
-

Acknowledgements / contributions: The data presented in this chapter were collected at the Miami Project to Cure Paralysis (University of Miami). Here, participants with spinal cord injury (SCI) were recruited by Yuming Lei, and Yuming and I collected the SCI dataset together. Many thanks to Monica Perez who oversaw and facilitated this collaboration, and Stuart Baker for making introductions. I was responsible for the design of the study, delivery of the protocol, analysis of the dataset, and completion of the discussion below, with valuable input from the aforementioned collaborators, as well as my supervisory team. Additional thanks to Helen Bosomworth for her effort and support on completing assessments. Finally, many thanks to the team at the Miami Project and everyone who took part in the study.

Sections of this chapter were previously reported in Hodkin et al. [1] © 2018 IEEE.

3.1 Introduction

Hebb's principle ("cells that fire together wire together" [86, 112]) suggests that the pairing of cortical and peripheral activity could strengthen intact descending pathways following neurological conditions such as stroke and spinal cord injury (SCI). If integrated into a therapeutic intervention, this could lead to improved motor function that is sustained after the intervention has been completed [23, 24, 94, 113, 114]. It has been proposed that the beneficial effects of functional electrical stimulation (FES) during rehabilitation may arise in part from neuroplastic changes in motor circuits [24, 115, 116], and that this therapeutic benefit of FES may rely on its pairing with appropriate descending commands [24].

Various research groups have reported promising results using such paired approaches [23, 71, 72, 74, 76, 105, 106, 109, 117], but the challenge remains to translate these often complex protocols into simple user-friendly devices suitable for intensive use in a clinical setting or at home. Additionally, to become commercially viable, devices must demonstrate efficacy, be cost effective, and be suitable for a wide range of people [64].

In this chapter, the findings of a feasibility study during which participants with cervical SCI completed a short intervention with the reaching and grasping device described in Chapter 2 are presented. The aim was to investigate if the device was suitable for the rehabilitation of the upper limb following SCI, with regards to usability, suitability of the task and any perceived benefits of a short training period.

3.2 Methods

3.2.1 Intervention and assessments

Participants with chronic SCI (≥ 6 months) were recruited to provide feedback on the device and complete a short intervention period. The study was completed at The Miami Project to Cure Paralysis, University of Miami, USA. It was approved by the local ethics committees and participants gave informed consent prior to joining the study and were reimbursed for the time spent completing the study.

Participants attended five sessions, typically on consecutive days with breaks as required. Sessions were scheduled to take one hour each, with a target of 200 repetitions per session. Three hours were scheduled for sessions at the start and end of the intervention to allow time to brief the participant, set-up the FES, perform assessments and to collect qualitative feedback.

Participants aimed to complete blocks of 20 to 25 repetitions followed by a one minute rest, although this was flexible to accommodate individual needs. At the start and end of each sessions participants completed 10 to 20 repetitions without stimulation.

The inclusion criteria were that participants had cervical SCI leading to mild, moderate or severe impairment of upper limb movement, aged over 18 years old and an Action Research Arm Score (ARAT) [111] score less than the maximum score of 57 on the side to be trained. It was also confirmed that participants could complete the task with FES assistance. Participants were excluded as per the stimulator manufacturer guidelines (e.g. poorly controlled epilepsy, an implanted electronic device such as a pacemaker, or pregnancy).

Participants were assessed before and after the intervention period using the Action Research Arm Test (ARAT). ARAT is a reliable and validated measure of upper limb function [81, 111] that involves the assessment of grasp, grip, pinch and gross movements on a scale of zero to three. The maximum score per arm is 57 and both arms were tested. The minimal clinically important difference (MCID) for ARAT is often set at 10% of the total score (≥ 6) [118]. To avoid bias, blinded videos were evaluated by an independent assessor who was not involved in delivering the intervention; this methodology has been previously established in stroke studies [119, 120]. Statistical testing was completed using a Wilcoxon's signed-rank test, with the null hypotheses that there was no change in ARAT score before and after the intervention, and that the change in ARAT score was the same for both the trained and untrained arm.

Participants were also asked to complete a questionnaire to collect qualitative feedback about the intervention. The questionnaires contained structured questions on upper limb function such as the strength and the range of movement before and after the intervention, and these questions were answered using a Likert scale. They were also asked if they would like to use the technology for rehabilitation, if they had benefited from the intervention and if they could use the technology independently. They were additionally provided with a section for general comments about the intervention.

3.2.2 Functional electrical stimulation (FES)

Asymmetric biphasic stimulation was applied using two pairs of disposable surface electrodes (PALS Neurostimulation Electrodes). The first pair (3.2cm round) extended the wrist, thumb and fingers, with the active electrode placed over the extensor digitorum communis (EDC), and the indifferent electrode over the extensor pollicis longus (EPL) and abductor pollicis

longus (AbPL). A second pair (5x5cm square) extended the arm at the elbow, with the active electrode on the anterior deltoid and the indifferent electrode on the triceps.

Stimulation parameters were individually set for each participant at the start of the study and checked for appropriateness before and throughout each session. Typically, only slight adjustment was required during the intervention period. Current values ranged from 20 to 35mA and stimulation pulse widths of 130 to 350 μ s were used. The stimulation frequency was fixed at 40Hz, and electrodes were positioned on the first day, with the position marked using a UV pen. These electrode positions were maintained for the duration of the study with little adjustment required.

As the participants had some residual upper limb function, the intention was to enhance this rather than overpower it, thus ensuring participants were actively involved in the task. Electrode positions were based on the manufacturer's guidelines [121] and adjusted to achieve the muscle activation that best resembled natural movement as observed by the experimenter and reported by the participant. The stimulation current was set at approximately 20mA and the pulse width increased until it produced a visible twitch in the index finger or arm. The pulse width was then increased to approximately 1.5 to 2.5 times this value as required to generate appropriate movement for the task. If this was not possible due to the maximum pulse width being reached, the current was increased and the process repeated.

The proximity sensors, which were fitted on adjustable sliders, were positioned for each participant to allow for different hand sizes and reaching trajectories, which may otherwise lead to incorrect triggering of the sensors.

3.3 Results

3.3.1 Task compliance & functional outcomes

Seven participants with traumatic SCI were recruited (mean age \pm SE = 37 \pm 6 years, 6 male, mean time since SCI 8 \pm 2 years, see Table 3-1). Two of participants with SCI were categorised on the American Spinal Injury Association (ASIA) impairment scale as AISA A (complete injury) due to no sensory or motor function being preserved in the sacral segments S4-S5 [16]. However, they were able to elicit some voluntary force below the neurological level of injury, indicating residual connectivity. All other participants were categorised as ASIA C (motor incomplete).

Table 3-1: Participants in this study

© 2018 IEEE [1].

ID	Age	Gender	NLI^a	ASIA^b	SCIM^c	Time since SCI (years)
1	20	M	C4	A	21	3
2	42	M	C4	C	30	9
3	20	M	C2	C	68	3
4	52	F	C5	C	99	14
5	57	M	C5	C	66	13
6	41	M	C7	C	64	4
7	29	M	C6	A	39	10

^a Neurological level of injury [16]

^b American Spinal Injury Association (ASIA) Impairment Scale [16]. ASIA A = complete, ASIA C = motor incomplete.

^c Spinal Cord Injury Measure (Version III, Self-report 2013) [122]

SCI participants completed approximately 1000 repetitions over the five days. All participants completed the full period, and as planned, sessions (excluding assessments) took approximately one hour. The hand / side best suited to completing the task with FES assistance, as agreed with the participant, was trained during the intervention, with the untrained side acting as a control.

Typically, stimulation to the forearm would open the hand, including finger, wrist and thumb extension. Stimulation to the shoulder and triceps would extend the arm at the elbow, but only aid elevation from the table – elevation was predominately achieved by the participant’s residual function. After an initial training and setup period, it was uncommon for incorrect triggering to result in inappropriate stimulation.

ARAT scores were assessed immediately before and after the intervention for both the trained and untrained limb (Figure 3-1). That is, following completion of the task on Day 5, the FES electrodes were removed and assessments were completed. The assessor did not note any significant reports of fatigue that may have influenced assessment outcomes. The mean (\pm standard error) improvement in ARAT score was 3.4 (\pm 1.1) on the trained side (Figure 3-2), and this change was statistically significant compared to the untrained side over the same period (0.1 ± 0.8 , paired two-sided Wilcoxon’s signed-rank test, $n=7$, $T^+=21$, $P=0.03$). One SCI participant showed an improvement that exceeded the MCID (≥ 6).

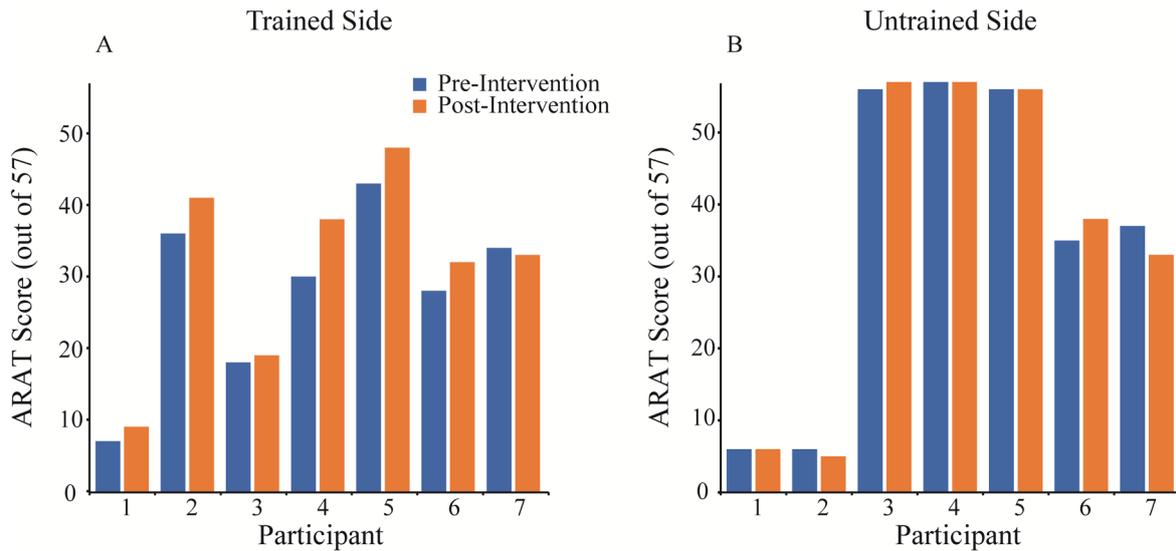


Figure 3-1: Individual ARAT scores for the trained and untrained sides before and after the intervention
 Panel A - The ARAT scores for the trained side for participants before and after the intervention. Panel B - The ARAT scores for the untrained side before and after the intervention. The maximum score is 57 per side. ARAT scores are as assessed by the blinded, independent assessor. For reference, the original assessor's scores for the before condition for participants 1 to 7 were (trained / untrained): 8 / 7, 35 / 5, 16 / 55, 27 / 57, 41 / 56, 30 / 34 and 35 / 39 respectively. Statistical testing between the original and independent blinded assessor on the trained side found a statistically significant correlation between the scores (Spearman Correlation $\rho=0.991$, $P=6.7 \times 10^{-12}$), but minimal agreement according to Cohen's Kappa ($\kappa=0.047$) [123]. This suggests both assessors captured the same trends, but had different interpretations of the scoring criteria. The original assessor was the same for all participants in this study. © 2018 IEEE [1].

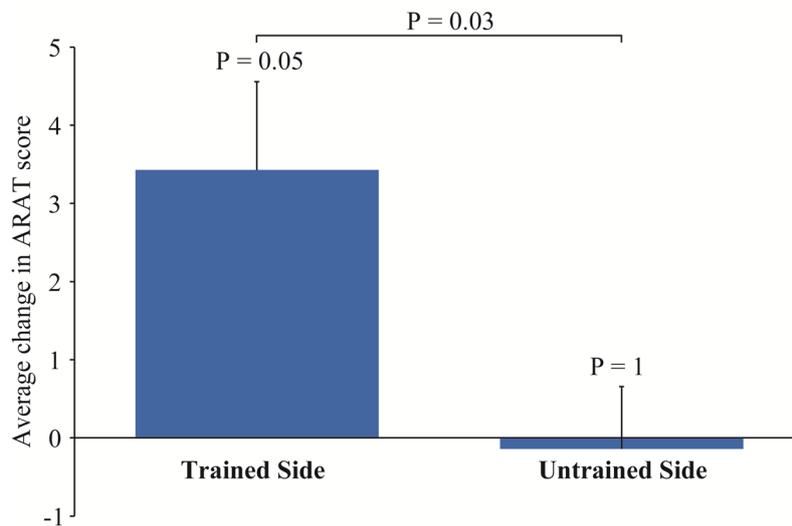


Figure 3-2: The mean change in ARAT score for the trained and untrained sides
 P values show the statistical significance measured using a two-sided Wilcoxon signed-rank test between the pre- and post-intervention assessments on the trained and untrained sides ($n=7$, $P=0.05$ $T+=26.5$ and $P=1$ $T+=5.5$ respectively), and between the two sides ($n=7$, $P=0.03$ $T+=21$). Error bars show standard error. © 2018 IEEE [1].

3.3.2 Qualitative feedback

Six out of seven of the participants reported that they had benefited from using the device, with five out of seven saying that they would use it again. Three participants reported benefits with activities of daily living such as holding a pen, drinking and cutting food subsequent to using the device. A selection of structured questions have been summarized in Figure 3-3.

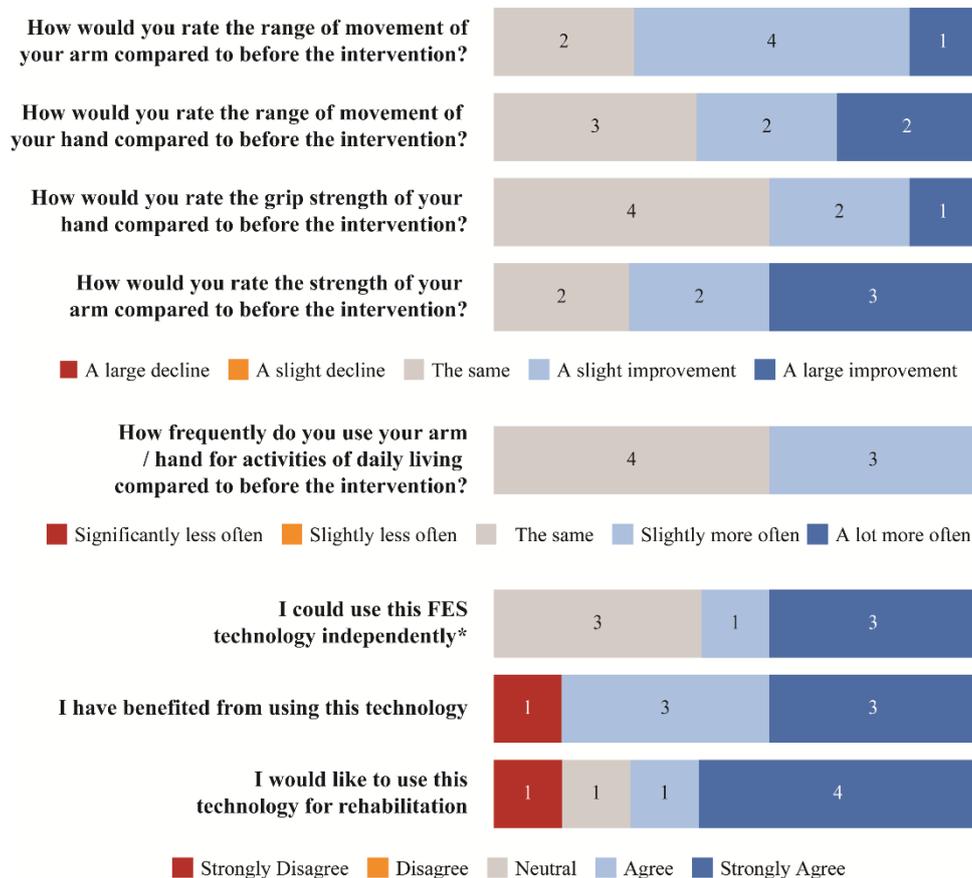


Figure 3-3: A selection of the qualitative data

Responses were collected using a Likert scale ($n=7$). *Participants often stated that they would require assistance with the set-up and the placement of electrodes, but could otherwise use the device independently. © 2018 IEEE [1].

3.4 Discussion

We have developed a neurorehabilitation device for reach-to-grasp movements that is suitable for use by selected participants with SCI. The intervention was well-tolerated and produced measureable changes in a general upper limb function test after training for 1 week. Participants showed good compliance with the task and achieved the target number of repetitions. The majority of participants reported that they had benefited from using the device.

Further studies will be required to establish whether additional benefits can be obtained through continued use of the device over extended periods of time, and to assess whether these benefits are maintained. We speculate that the functional improvements we observed may be due to neuroplasticity arising from the temporal contingency of voluntary motor commands and peripheral stimulation, as well as activity-dependent plasticity generated by completing a large number of repetitions of a task. However, additional investigations including neurophysiological testing and controls groups receiving FES or performing reaching movements alone will be required to support this hypothesis.

Improvement in ARAT scores amongst participants were modest in comparison to the MCID ≥ 6 [118], although one participant (#4) showed an improvement greater than this clinically significant threshold. As final evaluations were completed immediately after the intervention on day five, we cannot say how long-lasting effects were for the group. However, due to participant #4's improvement, they returned for a follow-up ARAT assessment one week after the intervention and it was found that the clinically significant benefit had been sustained. It should be noted that in some instances the untrained hand had high levels of function, and this limits the comparability of the trained and untrained sides before and after the intervention.

Participants with residual sensory and motor function below the neurological level of SCI were included in this study. It was predicted that the largest changes in function would be seen in those classed as ASIA C (motor incomplete), as there should be greater residual connectivity. Indeed, as anticipated, participants who had complete SCI (#1 and #7) showed little to no improvement in ARAT score, although participant #1 did verbally report feeling a benefit. Further studies will be required to establish optimal protocols for different severities of injury.

The reach and grasp movement can be broken down into three major components: (1) transporting the hand to the object, (2) the formation of the hand to grasp the object and (3) grasping the object [110]. One concern prior to this study was whether this simple configuration of cues and proximity sensors would be sufficient to accurately facilitate this complex movement. Auditory and visual cues were delivered simultaneously with the beginning of stimulation, therefore not accounting for any reaction time, which may have varied across trials and participants. As has been discussed in previous chapters, alternative approaches are to trigger stimulation using brain signals [124], EMG [72, 74, 106], accelerometers or other motion tracking [76, 109, 117] to correlate descending motor commands with peripheral stimulation. However, this increases the complexity and cost of such systems. In this study,

participants reported the stimulation to be a help rather than a hindrance to task completion, suggesting that the simple automated closed-loop system was capable of delivering stimulation with timing that was appropriately coordinated with a participant's intent. Furthermore, as will be explored in Chapter 5, the device has the capacity to provide stimulation at different timings relative to motor intent. Additional studies will be required to understand whether neuro-rehabilitative benefits can be improved by optimizing the stimulation timing.

3.5 Conclusion

This study has demonstrated the feasibility of a novel approach to closed-loop control of muscle stimulation for the rehabilitation of reach-to-grasp movements following SCI. Feasibility data with selected people with upper limb weakness following SCI, has demonstrated usability of the device, with positive feedback from users, and some modest functional benefits following a short intervention period. Further studies are required to establish clinical and cost effectiveness of longer durations of training, and to elucidate the mechanisms underlying functional improvements.

Chapter 4

Investigations into the utility of the device for upper limb rehabilitation following stroke

Aim:

- To investigate the utility of the novel device for upper limb rehabilitation following stroke.

Objectives:

- Obtain qualitative feedback from stroke survivors on the usability of the device, suitability of the task, and any perceived benefits from a short intervention
 - Use quantitative measures to assess any changes in function following a short intervention using the device
 - Investigate the importance of stimulation delivered concurrent with movement for device usability and efficacy, versus voluntary completion of the task with stimulation only applied during rest periods
 - Identify which groups of stroke survivors are likely to achieve the best outcomes with the device.
-

Acknowledgements / contributions: The data in this chapter were collected at two institutes: the Institute of Neuroscience, Newcastle University, and the Institute of Neurosciences, Kolkata (I-NK). For the feasibility study, stroke survivors at I-NK were primarily recruited by Supriyo Choudhury, and following training by me, the intervention was delivered by Isabel Glover and Jonathan Humby. I initiated and designed the extended intervention, and following training, it was delivered by master's students Ummatul Siddique and Simin Rahman (Amity University, Noida) at I-NK, and MRes student Colin Wan at Newcastle University. With my guidance, Ummatul presented the dataset collected at I-NK in her master's thesis, and Colin Wan the dataset he collected as a case study in his MRes thesis. For this, with my help, they completed their own analysis and interpretation of the datasets for this purpose. This chapter is the first time the combined dataset has been analysed. Many thanks to Hrishikesh Kumar who leads research at I-NK, and Robin Sengupta for making I-NK possible. Further thanks to Stuart Baker for supporting me on my first visit to I-NK. I recruited participants at Newcastle University, and also delivered the intervention. Thanks to Andrew Jackson and Helen Rodgers for their support during the study design and ethics process, and further thanks to Helen for making introductions to the relevant local support groups. With their help, I was responsible for the design of the study, coordinating with collaborators, training, analysis of the dataset, and completion of the discussion below. Additional thanks to Helen Bosomworth, Ravi Singh, Chris Price, Sarah Moore, and Damar Susilaradeya for their time, effort and support. Finally, many thanks to all the volunteers who took part in the study.

Sections of this chapter were previously reported in Hodkin et al. [1] © 2018 IEEE.

4.1 Introduction

Following stroke, and subsequent cell death, the motor system can be left impaired. Survivors may be limited in their ability to make voluntary movements and experience spasticity [8, 9, 125]. While there is some natural recovery, this is typically believed to plateau in the chronic stages (>6 months) [27]. Stroke survivors may develop compensatory strategies to complete activities of daily living, but it is the aspiration of research studies such as this, to develop therapeutic interventions that lead to behavioural restitution and true recovery [26]. To this end, we have developed the device presented in previous chapters which seeks to drive neural plasticity by pairing endogenous brain activity with stimulation of the peripheral motor system to improve rehabilitative outcomes.

This chapter reports the findings of a series of studies investigating the utility of the device for the rehabilitation of the upper limb in chronic stroke survivors. The chapter is divided into four parts. The first reports a feasibility study which obtained qualitative feedback from stroke survivors on the usability of the device, suitability of the task, and any perceived benefits following a two week intervention period. Quantitative measurements were also made to assess changes in function after training with the device.

Second, an extended study to investigate possible accrual of benefits with a longer intervention (four weeks) is reported. This was conducted to develop a better understanding of the time-course of functional changes, future recruitment criteria and to investigate possible plateau effects. Thirdly, a small cross-over study to investigate the utility of the device when stimulation is delivered during a rest period versus stimulation delivered concurrent with movement is presented. This was completed to understand of the importance of stimulation timing on qualitative and quantitative outcome measures.

Finally, data from all the aforementioned studies were combined to assess changes observed across this larger population, to improve our understanding of the characteristics of stroke survivors that may be best suited to using the device.

4.2 A feasibility study to investigate usability and possible benefits of using the device following stroke

4.2.1 Methods

4.2.1.1 *Intervention*

Participants with chronic stroke (≥ 6 months) were recruited to provide feedback on the device and complete a two week intervention. Participants attended 9 to 10 sessions, typically on consecutive days with breaks, such as weekends, as required. Sessions were scheduled to take one hour each, with a target of 200 repetitions per session. Three hours were scheduled for sessions at the start and end of the intervention to allow time to take consent, set-up the FES, perform assessments and to collect qualitative feedback. Participants aimed to complete blocks of 20 to 25 repetitions followed by a one minute rest, although this was flexible to accommodate individual needs. At the start and end of each session, participants would complete approximately 10 to 20 repetitions without stimulation.

The electrode positions, stimulation parameters and set-up procedure were previously reported in Chapter 3.

4.2.1.2 *Outcome measures*

Participants were assessed immediately before and after the intervention period using the Action Research Arm Test (ARAT) [81, 111]. They were also assessed at one week and one month following the end of the intervention. To avoid bias, blinded videos were evaluated by an independent assessor who was not involved in delivering the intervention. This methodology of using videos to assess ARAT has been previously established in stroke studies [119, 120].

Participants were also asked to complete a questionnaire to collect qualitative feedback about their views and experiences of using the device. The questionnaire was a mix of structured (Likert scale) and unstructured questions about the stimulation, appropriateness of the task and other suggested improvements or feedback.

4.2.1.3 *Participant recruitment*

The study was completed at two sites: the Institute of Neuroscience, Newcastle University (UK) and the Institute of Neurosciences, Kolkata (I-NK). It was approved by the respective local ethics committees at both centres and participants gave written informed consent prior to joining the study. Reimbursement of transport costs was offered at both sites.

The inclusion criteria were that participants had chronic stroke leading to mild, moderate or severe impairment of upper limb movement, aged over 18 years old, and an ARAT score less than 57 on their affected side. It was confirmed that participants could complete the task with FES assistance. Participants were excluded as per the stimulator manufacturer guidelines (e.g. poorly controlled epilepsy, an implanted electronic device such as a pacemaker, or pregnancy).

4.2.2 Results - Task compliance, functional outcomes & qualitative feedback

Four participants with stroke who met the inclusion criteria were recruited (mean age \pm SE = 50 \pm 6 years, 4 male, mean time since stroke 6 \pm 3 years, see Table 4-1). Two further participants were recruited, but were subsequently assessed to have an ARAT score of 57 by the independent, blinded assessor and therefore excluded from the analysis. Three participants received stimulation to open the hand only. One participant (#2) received additional stimulation to the anterior deltoid and triceps to extend the arm at the elbow.

Table 4-1: Participants in this study

Time since stroke is rounded to the nearest year. © 2018 IEEE [1].

ID	Age	Gender	Side of Weakness	Left / Right Handed	Time since stroke onset (years)
1	57	M	Left	Right	5
2	67	M	Right	Right	8
3	40	M	Left	Right	4
4	37	M	Right	Right	3

All four participants completed the study, however, the ARAT dataset for one participant (participant #4) was incomplete and has not been shown here. The qualitative feedback from this participant is included. Participant #1 completed the intervention on two occasions six months apart. Participants completed a total of 1800 to 2000 trials over the intervention period with each training session taking approximately one hour.

In the absence of spasticity or muscle tightness, stimulation to the forearm would open the hand, including finger, wrist and thumb extension, and stimulation to the shoulder and triceps would extend the arm at the elbow, but only aid elevation from the table – elevation was predominately achieved by the participant’s residual function. In the presence of spasticity and muscle tightness, finger, thumb and elbow extension were reduced and some ‘clawing’ of the

hand was observed. For the participants in this study, the stimulation was sufficient to aid them in completing the task.

Over the period of the intervention, ARAT scores improved by an average (\pm standard error) of 8 (± 3.1) (see Figure 4-1). Moreover, these improvements were maintained for one week (7 ± 4.5) and one month (7 ± 3.7) after the end of the intervention period. Two participants (#1 and #2) achieved the minimal clinically important difference (MCID) for ARAT (set at 10% of the total score (≥ 6) [118]), as shown in Figure 4-1. A clinically significant functional improvement was not found for participant #3. It is possible, that for this participant, the ARAT may not have provided appropriate sensitivity as their score was at the extreme end of the scale.

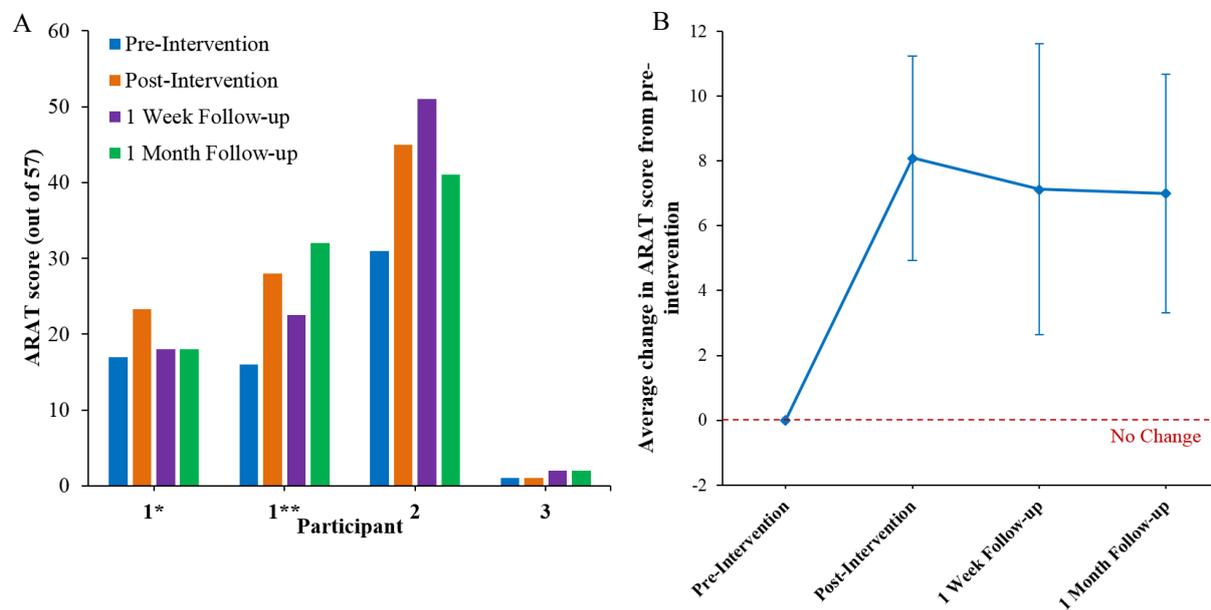


Figure 4-1: ARAT scores for participants in this feasibility study

Scores are as assessed by the blinded, independent assessor. Assessments were completed before the intervention period, immediately after, and 1 week and 1 month after the completion of the intervention. Due to the small sample size, statistical testing was not completed, but the minimal clinically important difference (MCID) for ARAT is often set at 10% of the total score (≥ 6) [118]. Error bars show standard error. * indicates visit 1 and ** indicates visit 2 for participant #1, which were separated by 6 months. Three different assessors completed the original ARAT assessments, but the same assessor completed all assessments for any particular participant. A strong correlation was found between the original assessors and the blinded assessor total scores (Spearman Correlation $\rho=0.951$), but no agreement in exact scores as measured using Cohen's Kappa ($\kappa=-0.16$) [123]. This suggests systematic differences between how the assessors interpreted the ARAT scoring, which meant that similar trends were captured, but not with the same score. For reference, the original assessor's scores for the pre-intervention assessments were: 10, 14, 29 and 3. Participant #4, who is not shown due to an incomplete dataset, had an original assessor score of 31. Panel A - © 2018 IEEE [1].

4.2.2.1 Qualitative feedback

All participants reported that they would use the device again. Two participants (#1 and #2) noted in an unstructured question that they had experienced functional improvements such as better movement in the hand, being able to pick up objects and ability to complete bimanual tasks. All participants agreed that the stimulation was comfortable and that it helped them move their upper limb in a useful manner during the task. Two participants asked for the device to be smaller / more portable. A selection of structured questions have been summarized in Figure 4-2.

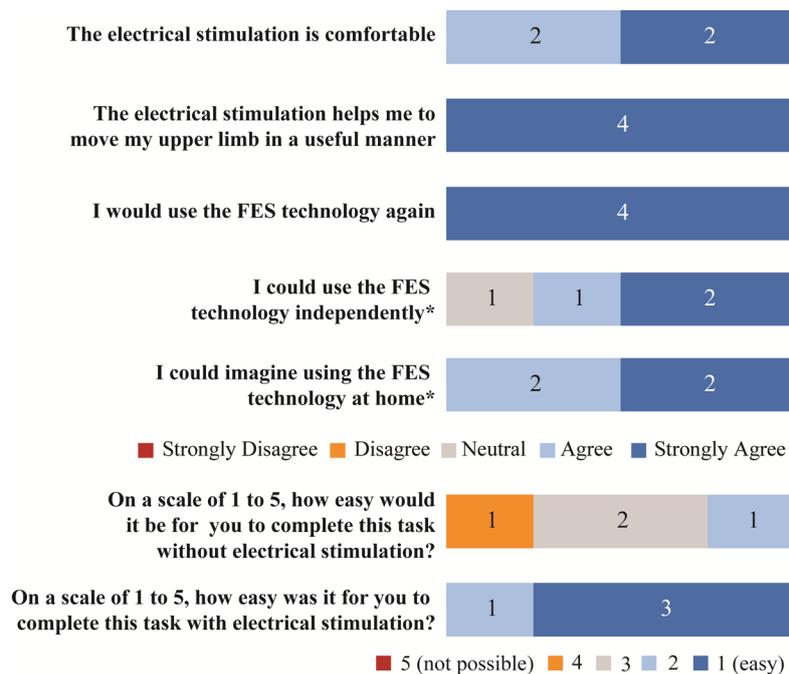


Figure 4-2: A selection of the structured qualitative feedback

The number of respondents was 4. Questions were answered on a Likert scale. *Participants often added the caveat that they would require training to use the device independently and / or at home. © 2018 IEEE [1].

4.2.3 Discussion of feasibility study

Two participants (#1 and #2) showed a clinically significant increase in function, which appeared to be sustained for participant #2. It is less clear for participant #1, as he completed two intervention periods and appeared to lose the measured functional gains following the first intervention period, but sustain them following the second. However, he did retain some hand function following the first intervention as measured by the grasping subsection of the ARAT assessment (pre-intervention 3/18, post-intervention 10/18, one week 7/18 and one month 8/18), but gains were offset by a drop in the scores in grip sub-section (pre-intervention 7/12, post-intervention 8/12, one week 5/12, one month 4/12).

The grasping function was retained at the start of the second intervention and continued to progress (pre-intervention 7/18, post-intervention 12/18, one week 14/18, one month 18/18), but gains were offset as the participant scored poorly in the grip subsection (pre-intervention 0/12, post-intervention 7/12, one week 0/12, one month 7/12) in both the pre-intervention and one week after assessments. This suggests that for this participant, the grip element of the ARAT may have been affected by other factors. While it is important not to draw strong conclusions from a single outcome measure for a small number of participants, there is some evidence for a carry-over effect, and the potential for activity dependent stimulation to lead to a carry-over effect has previously been reported [23, 24].

The two stroke participants (#1 and #2) that showed the clinically significant increase in function, initially scored in the mid-range of the ARAT. It could be inferred that participants with function within this range may benefit the most from using this device. Participant #3, who had a very low ARAT score, showed a very small change that was well below the MCID and could be attributed to other factors. A larger sample is required to understand the relationship between initial ARAT score and functional outcome, and to demonstrate the clinical effectiveness of this treatment.

4.3 An extended study to investigate the possible accrual of functional benefits with a longer intervention

4.3.1 Methods

This study was designed to replicate the two week feasibility study (see above), but over a four week period to investigate whether any measured improvements on functional assessments would accumulate with a prolonged training period. A target of 4000 repetitions was set for the four week period, with these being completed over the course of two to four sessions each week. Repetitions were typically completed in blocks of 100, with a total of 300-400 repetitions per session. However, this was flexible to allow participants to self-pace the intervention. Furthermore, this was an increase on the blocks of 20 previously used, which some participant had found frustrating as it disrupted their rhythm and slowed down delivery of the intervention. At the start and end of each session, participants would complete approximately 10 repetitions without stimulation. For practical reasons, i.e. time frames available at I-NK, a baseline period was not possible for this study. The details of the intervention and assessments are shown in Figure 4-3.

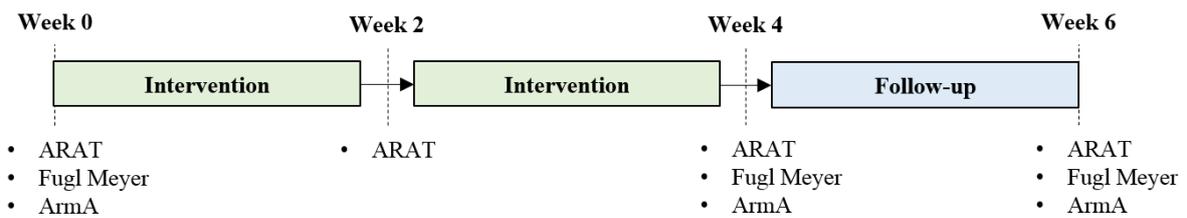


Figure 4-3: The intervention and assessment timings for the extended intervention Outcome measures (ARAT, Fugl Meyer, and ArmA) are described below.

4.3.1.1 Study location & participants

The study was completed at two sites: the Institute of Neuroscience, Newcastle University (UK) and the Institute of Neurosciences, Kolkata (I-NK). It was approved by the respective local ethics committees and participants gave written informed consent prior to joining the study. Reimbursement of participant transport costs was offered at both centres.

Participants were recruited through local support groups, word-of-mouth and by the research team at the Institute of Neurosciences, Kolkata (I-NK). Inclusion and exclusion criteria were as per the feasibility study reported above.

4.3.1.2 Task & functional electrical stimulation

FES was delivered using the device as previously described (see Chapter 3). However, to widen accessibility, a Saebo MiniMAS (Saebo Inc.) support arm was made available to participants at Newcastle University. This is a zero gravity support arm that supports reaching movements.

Stimulation was delivered at 40Hz, with currents ranging between 21 and 35mA, and pulse widths 110 and 310 μ s. Stimulation settings were checked at the start of each session for comfort, hand opening and arm extension. While stimulation settings were typically kept consistent between intervention periods and within sessions, to ensure comfort and suitable muscle activation, modifications in electrode position and intensity were made.

The distance reached during the task was adjusted for each participant, and typically kept constant throughout the intervention period, although occasional adjustment was required to maintain comfort and to keep the task challenging.

4.3.1.3 Outcome measures

The primary outcome measure was the Action Research Arm Test [81, 111], which was assessed immediately before the intervention, and then at two weeks, four weeks and following

a two week follow-up period, as shown in Figure 4-3 (above). The secondary outcome measures were the Fugl Meyer (FM) assessment, and the Arm Activity Measure (ArmA). These were completed immediately before the intervention, at four weeks and following the two week follow-up period. Further secondary outcomes were reported Ummatul Siddique's and Colin Wan's masters theses, but due to the small sample size and inconsistencies in data collection between centres, these have not been presented here.

The ARAT (see Chapter 2) has previously been described. The Fugl-Meyer (FM) assessment is a stroke specific functional assessment [126]. It can be used to assess the upper and lower limb, but only sections relevant to the upper limb were used. It measures voluntary and passive joint movement, reflex activity and sensation, and has been validated and recommended as a clinical and research tool [127]. The Arm Activity Measure (ArmA) was developed by Stephen Ashford and colleagues at King's College London & Regional Rehabilitation Unit, Northwick Park Hospital, London [128]. Participants are asked to respond to a series of questions on a five point ordinal scale. Section A is related to caring for the affected hand, and Section B is about independently completing activities of daily living with the affected hand. Section A and B are treated separately, and lower scores are associated with greater function. The ArmA provides a useful self-reported measure of function following an upper limb intervention.

Statistical testing was completed in IBM SPSS 24. Due to the small sample size, this was typically completed using non-parametric tests. For pairwise statistical tests, the null hypothesis was that there was no significant difference between either the interim (where applicable), post-intervention or follow-up ARAT score and the pre-intervention ARAT score.

4.3.2 Results - Task compliance & functional outcomes

Six participants (6 male, 46 ± 6 years old (mean \pm SE)) were recruited onto the study. The mean time since stroke was 4 ± 1.6 years (see Table 4-2). Participants #1 and #2 had completed the cross-over study described below prior to taking part in this study (as participants #3 and #5 respectively). Participant #5 had previously completed the feasibility study described above (as participant #3).

Five of the six participants recruited completed the intervention. Participant #1 was unable to complete the study due external difficulties with travel arrangements, and this incomplete dataset has been omitted. The support arm was used by one participant (#2) for the first two weeks of the intervention. All participants received stimulation to both open the hand and

extend the arm, except for one participant (#4) who received stimulation to facilitate hand opening only for the first six sessions.

All participants completed 4000 repetitions over the four week period. These were typically completed during two to four sessions per week. Sessions were usually divided into blocks of 100 repetitions, but this was varied depending on individual needs and preferences.

ARAT scores are presented in Figure 4-4, and Fugl Meyer scores are split into three sub-sections: function (Figure 4-5), passive range of motion (Figure 4-6), and sensation (Figure 4-7). The ArMA scores are split into the assessments two sub-sections: Section A – caring for the affected hand (Figure 4-8), and Section B - ability to independently complete tasks or activities using the affected arm (Figure 4-9). All scores are those given by the original assessor.

Table 4-2: Participants in this study

Time since stroke is rounded to the nearest year.

	Age	Gender	Time Since Stroke (years)	Side of Weakness	Left / Right Handed
1	35	M	1	Left	Right
2	62	M	11	Left	Right
3	66	M	1	Right	Right
4	34	M	2	Right	Right
5	40	M	4	Left	Right
6	40	M	2	Right	Right

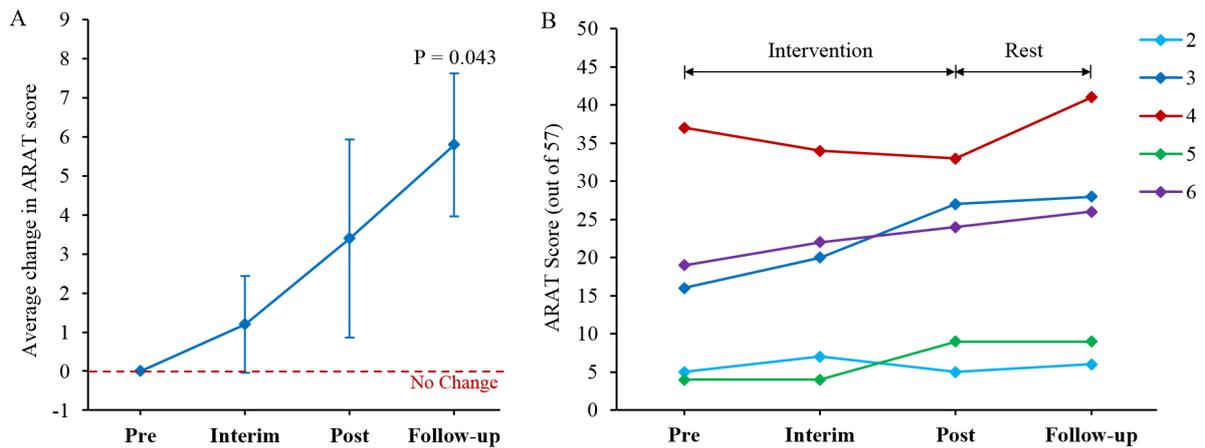


Figure 4-4: Changes in ARAT score

Panel A - Average change in ARAT score ($n=5$) halfway through the intervention (interim (2 weeks)), post-intervention (1 month) and following an approximately 2 week rest period, compared to before the intervention. Panel B - Individual ARAT scores over the intervention and follow-up period. The maximum ARAT score is 57. MCID for ARAT is often considered to be ≥ 6 [5]. A related samples Friedman's test on the change observed at each time point did not find a significant difference across the groups ($P=0.143$). A Wilcoxon sign-rank test was performed and showed a change in ARAT score between the pre-intervention score and that measured at the two week follow-up ($P=0.043$), but this was not significant following a Bonferroni correction for multiple comparisons ($P_{sig}<0.017$).

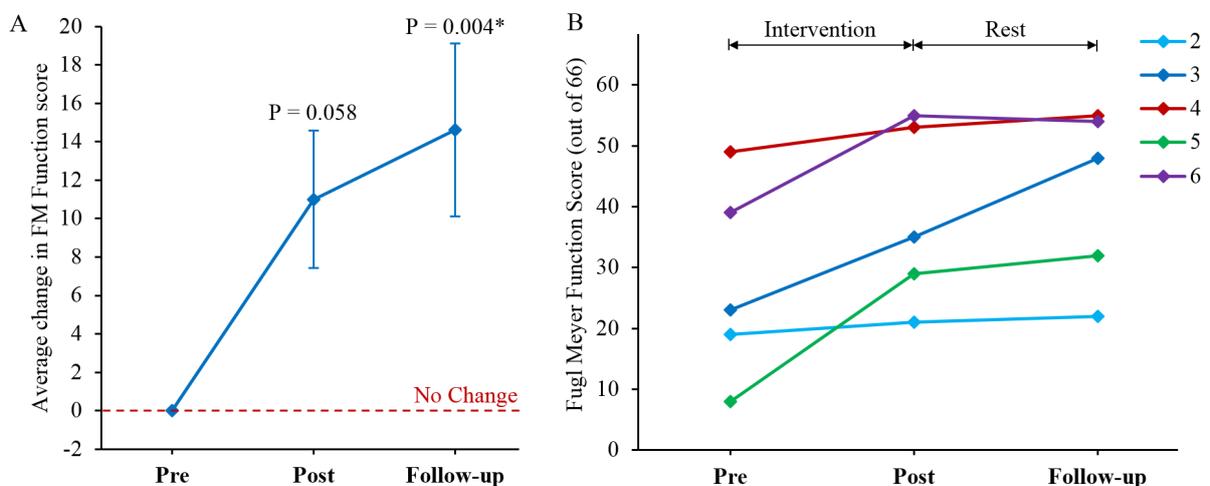


Figure 4-5: Change in Fugl Meyer upper extremity function score

Panel A - Average change in Fugl Meyer upper extremity function scores ($n=5$) post-intervention (1 month) and following an approximately 2 week rest period, compared to the pre-intervention assessment. Panel B - Individual Fugl Meyer upper extremity function scores. The maximum score for this section is 66. A related-samples Friedman's test was conducted on the scores at each time point and a significant difference found ($P=0.015$). Subsequent pairwise post-hoc testing (Dunn test) found a significant difference between the 'pre' and 'follow-up' measurements ($P=0.004$), which is significant after a Bonferroni correction ($P_{sig} = 0.025$). A comparison between 'pre' and 'post' measurements was not significant $P = 0.058$.

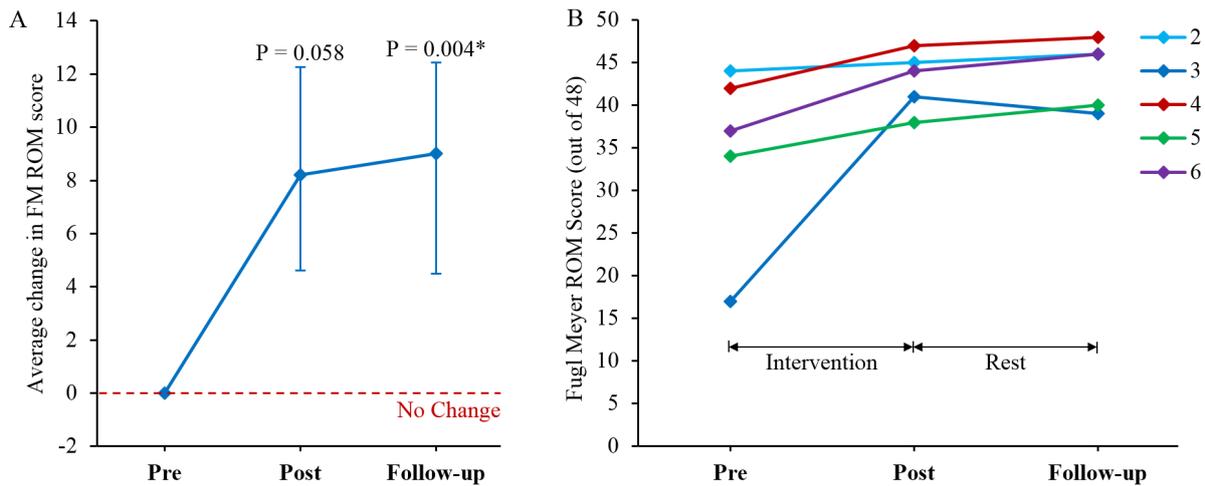


Figure 4-6: Change in Fugl Meyer upper extremity passive range of motion (ROM) score

Panel A - Average change in Fugl Meyer upper extremity passive ROM scores ($n=5$) post-intervention (1 month) and following an approximately 2 week rest period, compared to the pre-intervention assessment. Panel B - Individual Fugl Meyer upper extremity passive range of motion scores. The maximum score for this section is 48. A related-samples Friedman's test was conducted on the scores at each time point and a significant difference found ($P=0.015$). Subsequent pairwise post-hoc testing (Dunn test) found a significant difference between the 'pre' and 'follow-up' measurements ($P=0.004$), which is significant after a Bonferroni correction ($P_{sig} = 0.025$). A comparison between 'pre' and 'post' measurements was not significant $P = 0.058$.

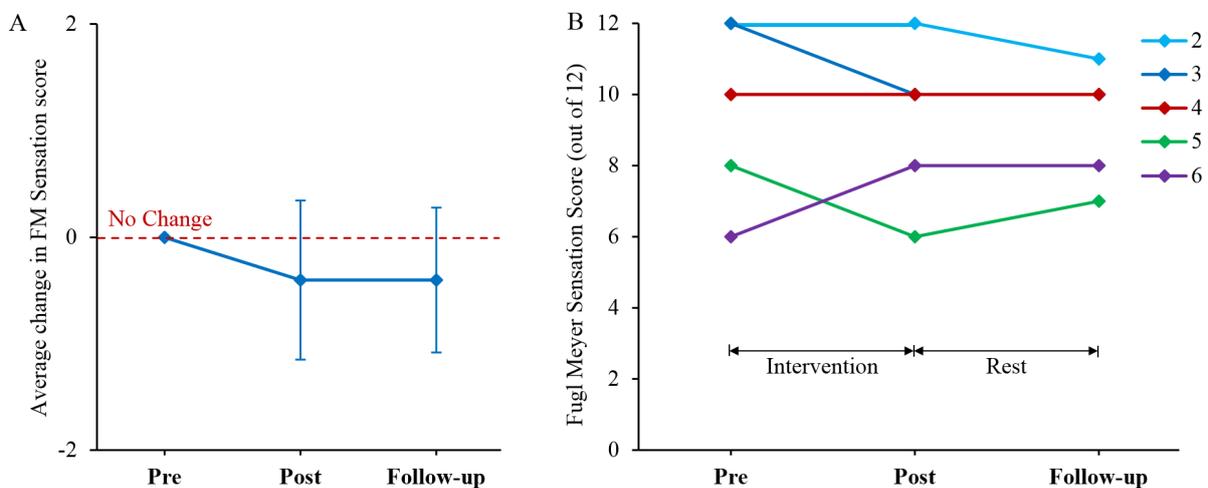


Figure 4-7: Change in Fugl Meyer upper extremity sensation score

Panel A - Average change in Fugl Meyer upper extremity sensation scores ($n=5$) post-intervention (1 month) and following an approximately 2 week rest period, compared to the pre-intervention assessment. Panel B - Individual Fugl Meyer upper extremity sensation scores. The maximum score for this section is 12. A related-samples Friedman's test was conducted on the scores at each time point and no statistically significant difference was found ($P=0.584$).

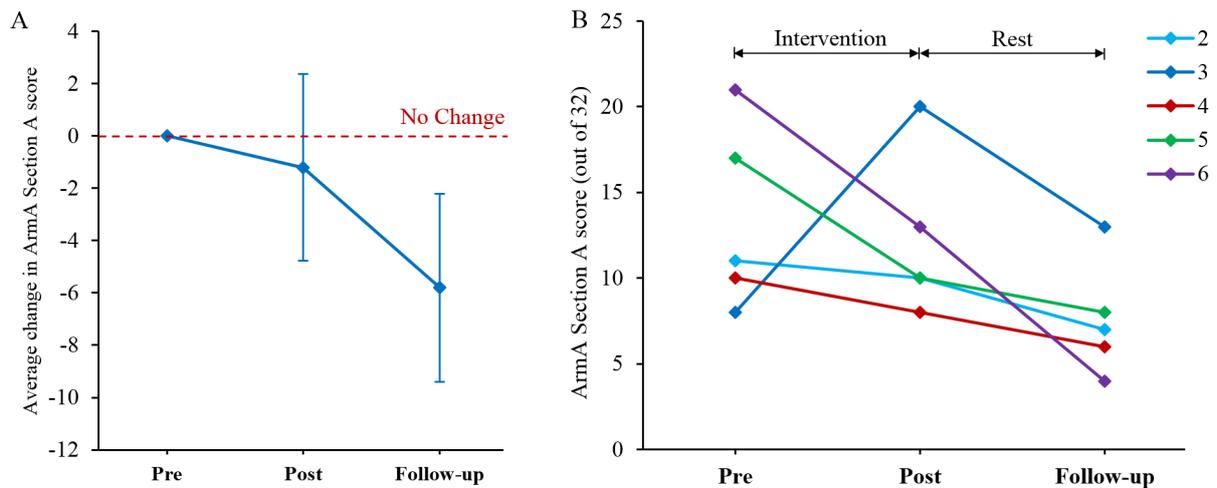


Figure 4-8: Change in ArmA Section A score

Lower scores are associated with improved ability to care for the affected arm. Panel A - Average change in ArmA Section A ($n=5$) post-intervention (1 month) and following an approximately 2 week rest period compared to the pre-intervention assessment. Panel B - Individual ArmA Section A scores. The maximum score is 32. A related-samples Friedman's test was conducted on the scores at each time point and no statistically significant difference was found ($P=0.074$).

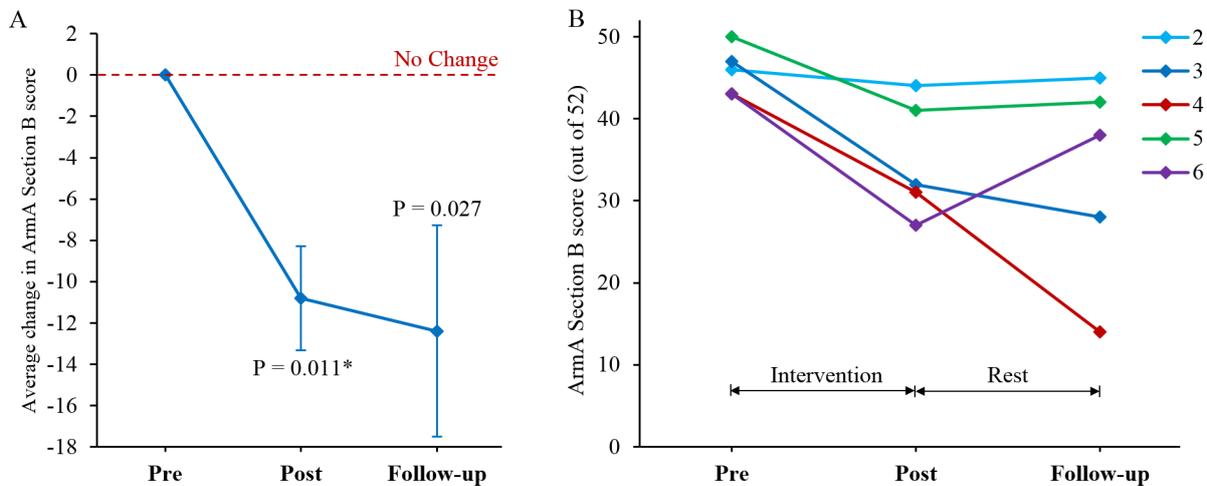


Figure 4-9: Change in ArmA Section B score

Lower scores are associated with improved ability to independently complete tasks or activities using the affected arm. Panel A - Average change in ArmA Section B ($n=5$) post-intervention (1 month) and following an approximately 2 week rest period, compared to the pre-intervention assessment. Panel B - Individual ArmA Section B scores. The maximum score is 52. A related-samples Friedman's test was conducted on the scores at each time point and a significant difference found ($P=0.022$). Subsequent pairwise post-hoc testing (Dunn test) found a significant difference between the 'pre' and 'post' measurements ($P=0.011$), which is significant after a Bonferroni correction ($P_{sig} = 0.025$). A comparison between 'pre' and 'follow-up' measurements was not significant $P = 0.027$ after correction for multiple comparisons.

4.3.3 Discussion of the extended intervention

This study showed that for participants who respond to the intervention, improvements in ARAT score may accumulate over a four week training period (Figure 4-4). Individual scores suggested that the effect was most prominent for participants with ARAT scores in the mid-range, where both participants (#3 and #6) improved by more than the Minimum Clinically Important Difference (MCID ≥ 6) [120] (+12 and +7 respectively). Repeated baseline assessments were not possible for participants at I-NK, but as participants are chronic stroke survivors, it is unlikely the improvements observed were spontaneous or exclusively caused by on-going natural recovery. It is interesting to speculate whether these changes would continue with a longer intervention, and whether participants would continue to engage with the task for a longer period. Participants at I-NK requested an additional two weeks of training at the end of the protocol, and while the findings are outside the scope of the study reported here, it demonstrated some participants would be willing to complete longer interventions. Furthermore, as described in the introduction to this thesis, Mann et al. showed improvements on the ARAT after 6 and 12 weeks of training using their FES intervention, with the improvements at 6 weeks approximately half those found at 12 [80]. This suggests that some FES protocols can show continued improvements on the ARAT over prolonged training periods.

To check for inter-assessor variations, videos of the ARAT assessments from I-NK were blinded and assessed by the Newcastle assessor. Due to difficulties with videos for the pinch sub-scale and a different interpretation of the gross movement task, only scores for the grip and grasp sub-scales were directly comparable. The I-NK assessor found an average improvement of 2.25 (grip + grasp) and the blinded assessor an average improvement of 2.0 at the two week follow-up compared to before the intervention, suggesting good agreement. A strong correlation between the assessors total scores for these two sub-sections was found (Spearman Correlation $\rho = 0.967$, $P=3.6 \times 10^{-12}$), but a small Cohen's Kappa score ($\kappa=0.255$) indicated minimal agreement in exact scores [123]. This suggests that while overall trends are the comparable, there could be systematic differences between assessors, such as interpretation of the scoring criteria. It is important that future trials ensure consistent training and interpretation of test scoring between assessors, and that where possible, assessors are blinded to the study treatment to avoid possible bias. There was a notable disagreement between the two assessors at one month for participant #4, which might account for the unusual drop seen in Figure 4-4. Some of the greatest improvements observed by original assessor were in the pinch sub-scale,

hence the large discrepancy between the average change in combined grip and grasp scores (2.25) and the overall change in score shown in Figure 4-4.

Like the ARAT, the Fugl Meyer (FM) function and passive range of motion scores showed accumulating improvements across the intervention and subsequent rest-period (Figure 4-5 and Figure 4-6), with significant changes in the FM function score at the two week follow-up assessment. Of note, is the individual plot for participant #5, who only showed limited improvements on the ARAT, but a much larger change on the FM function assessment (Figure 4-5). Improvements for this participant were below the MCID for ARAT, but the changes in FM function were above levels considered real and meaningful (6 to 8) [129]. Whilst further investigations are required, this might indicate that future recruitment and outcome measures should not be based on ARAT score alone, as ARAT may not be capturing all the changes observed. The FM sensation scores did not see any significant changes (Figure 4-7), which was not unexpected as the intervention primarily targets function and range of movement.

Decreases in score were observed for both section A and section B of the ArmA (Figure 4-8 and Figure 4-9), which indicates an improved ability to care for the affected hand (Section A) and improvements in the independent completion of activities of daily living (Section B). It should be noted that the assessors at I-NK reported that the questions did not always translate well, and this is a consideration for future studies. Similarly, participants in the UK were at times confused by interpretation of questions, which might lead to inconsistent scoring. Whether this is a problem with the assessment or delivery of the assessment needs to be investigated.

Overall, while this dataset is limited in size, the outcome measures suggest that for some participants, improvements may accumulate with longer intervention periods and over subsequent rest periods, and that the FM and ARAT can offer different insights into possible functional changes.

4.4 A study to investigate the utility of the device when stimulation is delivered during a rest period vs. delivery concurrent with movement

4.4.1 Methods

4.4.1.1 *Intervention and assessments*

In this study, participants were invited to complete two interventions. The first, was to complete the task as previously described in the feasibility study above, i.e. stimulation concurrent with

voluntary movement for a two week period ('stimulation with movement'). The second, was to complete the task using voluntary motion alone with stimulation delivered during the rest periods between trials ('stimulation during rest'). Both intervention periods were for two weeks, with a two week baseline period in between which also acted as a follow-up period for the first intervention, as shown in Figure 4-10.

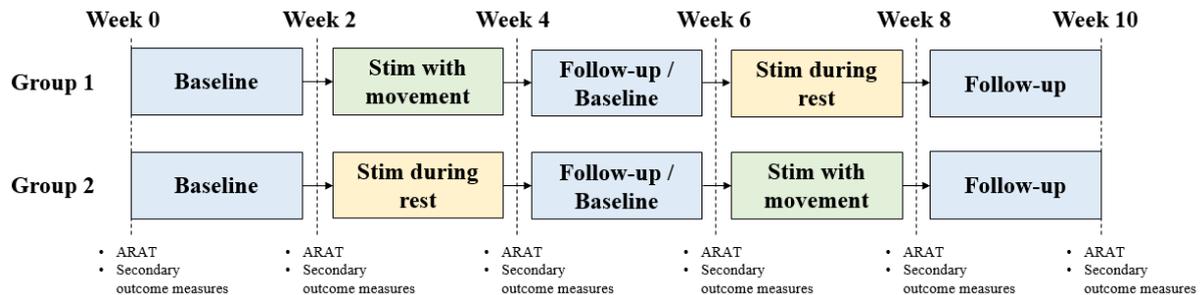


Figure 4-10: The interventions and assessments delivered in this study

A target of 2000 repetitions was set for each intervention, with repetitions typically completed in blocks of 100, with a total of around 300 repetitions per session. At the start and end of each session, participants would complete approximately 10 repetitions without stimulation. A cross-over design was used to counter any possible carry-over effects, and participants were alternately placed into two groups in the order they were recruited.

4.4.1.2 Recruitment

Participants were recruited from local stroke groups, from previous studies, by an advert and through distribution of an information sheet. Participants fulfilled the inclusion / exclusion criteria as described previously. The study was completed at the Institute of Neurosciences, Newcastle University. The study was granted ethical approval by Newcastle University's Faculty of Medical Sciences Ethics Committee, and reimbursement was offered for participant travel costs.

4.4.1.3 Functional electrical stimulation

The 'stimulation with movement' condition was delivered as previously described. Stimulation for the 'stimulation during rest' condition was delivered in two bursts during the five second rest period between trials. These two bursts represented the reaching and releasing phases of the task. This is shown in Figure 4-11.

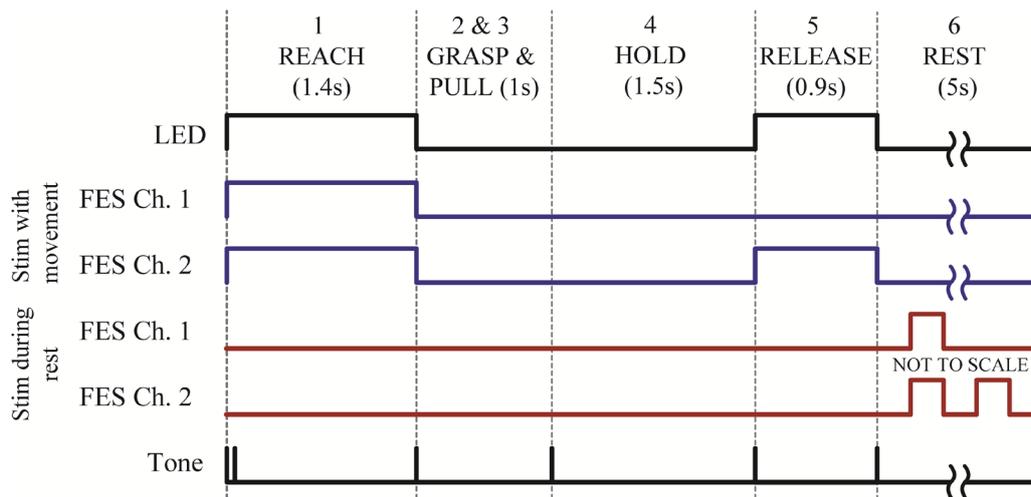


Figure 4-11: The ‘stimulation during rest’ condition

The ‘stimulation during rest’ condition (red) compared with the conventional stimulation protocol (blue). The stimulation is not shown to scale and the time periods were 1.2 and 0.9s respectively to match the reach and release phases in the ‘stimulation with movement’ condition.

The time-periods for these two bursts of stimulation were determined using data collected during the feasibility study reported above. This included the two participants that were excluded from the study for having an ARAT score greater than 57 (as assessed by the independent blinded assessor). Twenty repetitions from the mid-point of that study were analysed for these six participants. The average times for the reach and release phases were found to be 1.2 ± 0.1 s and 0.9 ± 0.0 s (mean \pm SE) respectively. Subsequently, stimulation was delivered during the rest period as follows: 1s rest, 1.2s FES, 1s rest, 0.9s FES, 0.9s rest. The total ‘rest’ period therefore remained 5 seconds.

Stimulation was delivered at 40Hz, with currents ranging between 25 and 43mA, and pulse widths 180 and 350 μ s. Stimulation settings were checked at the start of each session for comfort, hand opening and arm extension. While stimulation settings were typically kept consistent between interventions and within sessions, to ensure comfort and suitable muscle activation, modifications in electrode position and intensity were made. The distance reached during the task was adjusted for each participant, and while this was typically kept constant throughout the intervention, occasionally adjustments were made to maintain comfort and to keep the task challenging.

To widen accessibility, initially a custom support arm and later a Saebo MiniMAS (Saebo Inc.) support arm were made available to participants. Additionally, if it was not possible for a participant to complete the task without stimulation, an alternative ‘stimulation during rest’ task was developed. Here, the participant would reach and grasp a cloth placed on the table and

pull it back towards themselves, replicating a commonly used physiotherapy task. This enabled them to slide rather than lift the arm during the reaching and pulling phases of the task.

4.4.1.4 *Outcome measures*

The primary outcome measure was the Action Research Arm Test (ARAT) [81, 111], assessed two weeks before the start of the intervention, before and after each intervention, and following a two week rest period, as shown in Figure 4-10 (above). A range of additional secondary outcome measures, assessed at the same time points, were used. These included: Arm Activity Measure (ArmA), the Box and Block Test [130], and maximum pinch and power grip force. Participants also completed a questionnaire of predominately structured questions (Likert Scale) to provide qualitative feedback on the two interventions. Statistical testing between measurements at different time points was completed in IBM SPSS 24. The first null hypothesis tested was that the change in ARAT score measured during the intervention, or following the follow-up period, was not significant compared the change in ARAT scored measured during the baseline period. This was conducted for both the intervention and control groups. The section null hypothesis, referring to pooled data from both the control and intervention group, was that there no significant difference between changes in ARAT during the intervention and changes in ARAT measured during the baseline period.

A Hand Dynamometer (HD-BTA, Vernier Software & Technology, LLC.) with a custom interface using a National Instruments card and MATLAB software (The MathWorks, Inc.) was used to measure pinch and power grip strength. The Box and Block Test is a commonly used unilateral assessment of manual dexterity [130].

4.4.2 Results

Of the nine volunteers that completed an initial assessment, five went on to be enrolled onto the study (age 58 ± 6.5 years, time since stroke 6 ± 1.5 years (mean \pm SE)). Those excluded typically did not have suitable levels of impairment for the task. Participant #1 had previously taken part in the feasibility study (as participant #2). Participant details are shown in Table 4-3.

Participant #5 completed both interventions with the support arm, and participant #4 completed the ‘stimulation with movement’ intervention with the support arm and the ‘stimulation during rest’ intervention using the alternative methodology described above. Additionally, for participant #4, a non-slip surface (Dycem Ltd.) was attached to the block to assist with gripping the block during the ‘stimulation with movement’ intervention.

Table 4-3: Participants in this study

Time since stroke is rounded to the nearest year. Group refers to those shown in Figure 4-10.

	Age	Gender	Time Since Stroke (years)	Side of Weakness	Left / Right Handed	Group
1	68	M	8	Right	Right	2
2	69	M	5	Left	Right	2
3	35	M	1	Left	Right	1
4	54	F	5	Left	Right	1
5	62	M	11	Left	Right	2

All participants completed the full intervention. The average (\pm SE) number of repetitions for the ‘stimulation with movement’ and ‘stimulation during rest’ conditions was 2021 ± 26 and 1961 ± 81 respectively. This discrepancy was due to participant #4 who completed 300 less repetitions in the ‘stimulation during rest’ condition due to adverse weather (snow) leading to the cancellation of a training session which could not be rescheduled. Participants #1 and #3 had approximately three to four week between interventions due to adverse weather (snow) and other external factors. Participants completed sessions of varying length, but typically between 300 and 400 repetitions per session in blocks of 100. Participants received stimulation to both open the hand and extend the arm, except for participants #2 and #4 who received stimulation to facilitate hand opening only. Participant #2 reported receiving Botulinum toxin injections during the intervention, and participant #4 reported receiving Botulinum toxin injections prior to the intervention, both of which may act as confounding factors. Similarly, participants also reported the intermittent use of splints during the intervention that may also have a confounding effect.

It was not possible for all participants to complete the pinch force test due to difficulties gripping the device. Power grip force, Box and Block and ArmA did not show significant changes and the data are not shown. Changes in ARAT score are shown in Figure 4-12, and a combined analysis of both interventions versus the baseline period is shown in Figure 4-13. In addition to structured qualitative feedback shown in Figure 4-14, unstructured qualitative feedback gave insights into the nature of changes observed by participants. This is captured in Table 4-4. Note that this feedback is not necessarily intervention specific, but often represents general comments from throughout both interventions.

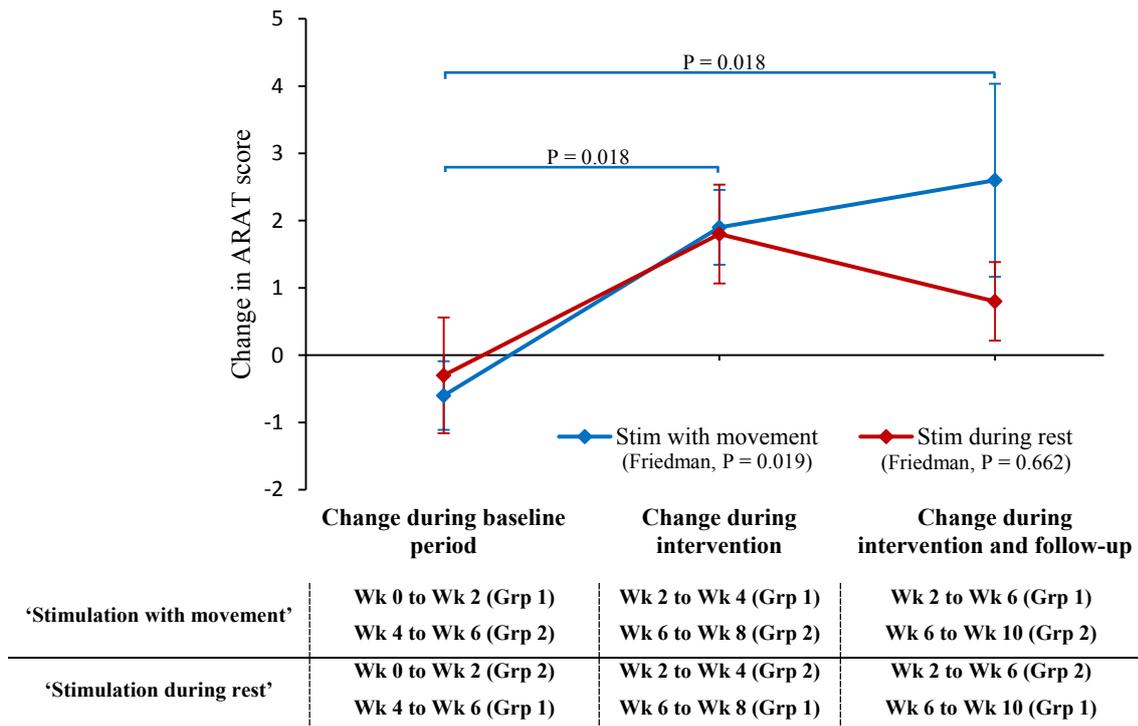


Figure 4-12: A comparison of the changes in ARAT score observed in the two conditions tested

A comparison between the changes in ARAT score in the 'stimulation with movement' and 'stimulation during rest' conditions. See Figure 4-10 for intervention timings. Error bars show standard error. The number of participants was 5. Statistical testing was completed using a related samples Friedman's test. A statistically significant difference was found between the 'stimulation with movement' groups ($P=0.019$), and post-hoc testing (Dunn test) found the P values shown in the figure. A Bonferroni correction for multiple comparisons was applied, and therefore $P_{sig} = 0.025$, making the pairwise comparisons significant. No statistically significant difference was found between the 'stimulation during rest' groups ($P=0.662$), or between the two interventions (change in ARAT score) at the end of follow-up period (Wilcoxon signed rank, $P=0.197$). Test results should be interpreted with caution due to the small sample size.

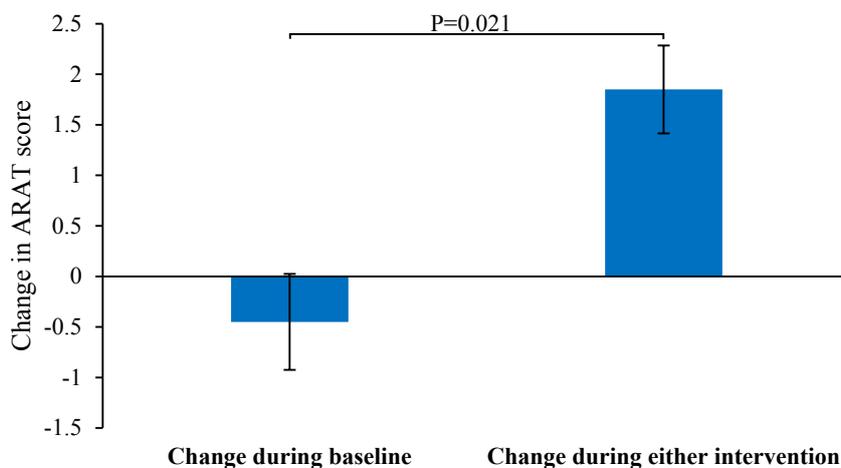


Figure 4-13: The combined average change in ARAT score during either intervention vs. baseline

The combined average change in ARAT score during the 'stimulation with movement' and 'stimulation during rest' versus the average change during a baseline period. Statistical testing was completed using a Wilcoxon signed-rank test, $P<0.05$ is considered statistically significant.

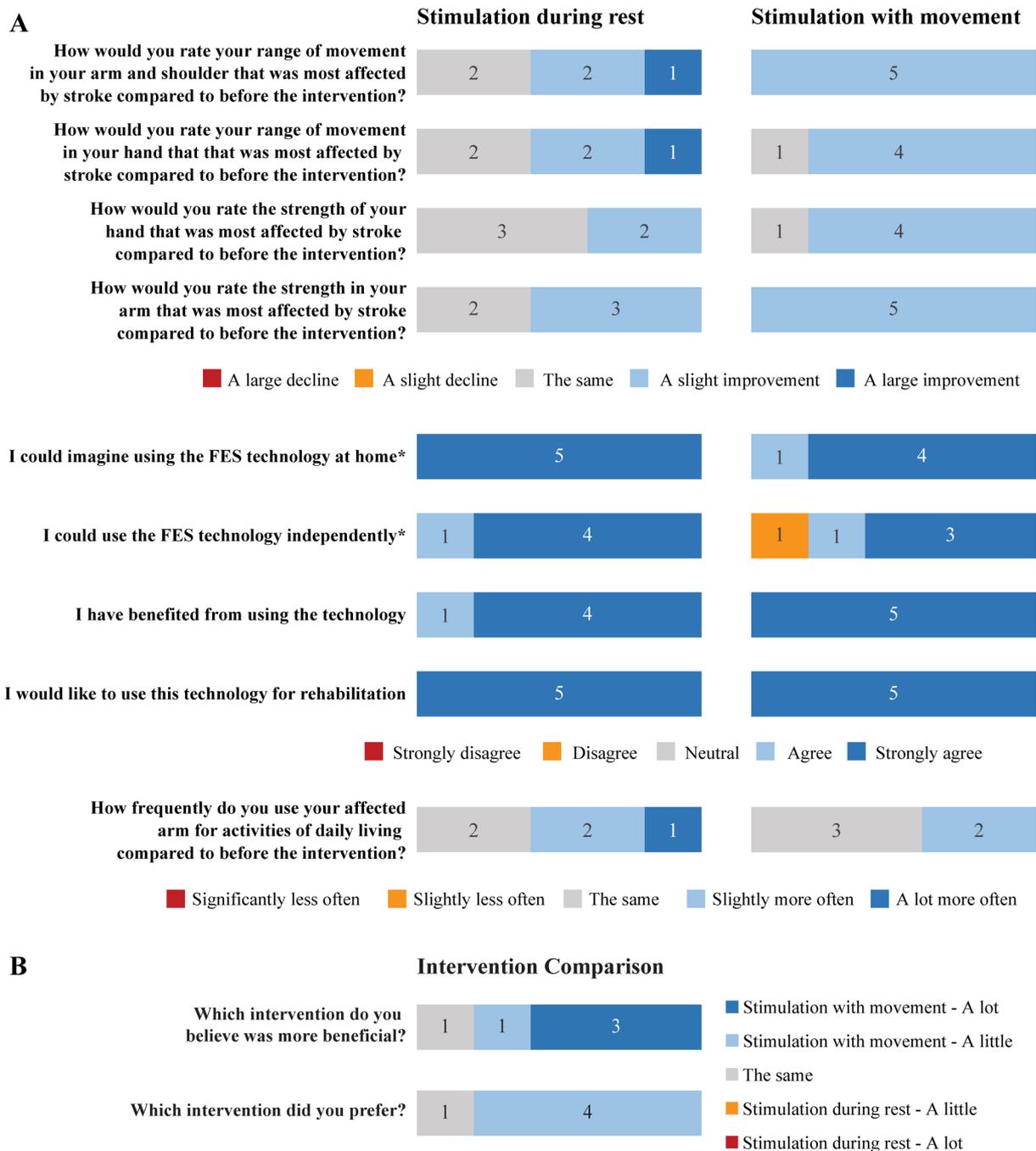


Figure 4-14: A selection of qualitative feedback collected during the study
 Panel A - Qualitative feedback collected during the two interventions (n=5). Panel B - A comparison of the two interventions (n=5).

Table 4-4: Participant reported comments and observations from the study

Note that comments were often general to the entire study and not intervention specific.

Participant	Comments / observations
1	<ul style="list-style-type: none"> - Improvements in ADLs such as: filling the kettle, reaching wall units, acknowledging other road users, lifting a bag into the bin and using light switches. - Changes are incremental and hard to immediately detect - Improved dexterity, suppleness and control - Increased confidence and changed ‘state of mind’ – reminded to use more affected limb.
2	<ul style="list-style-type: none"> - Modest improvements in ADLs such as using a fork to eat, and an increased range of movement when reaching bannisters on the stairs and placing hands on the car steering wheel.
3	<ul style="list-style-type: none"> - Hand, arm and wrist felt looser during the ‘stimulation with movement’ condition - During the two week period between interventions, woke-up one day and the affected hand was notably looser than ever before. The change was sustained, and subsequently started trying to zip up fleece.
4	<ul style="list-style-type: none"> - Some improvements in shoulder looseness and range of movement at the end of the study - Hand had felt tighter following the inter-intervention rest, but returned to normal during the second intervention.
5	<ul style="list-style-type: none"> - Improved hand colour during the interventions - it was not getting as cold - Affected arm was more relaxed at night and during gardening, and it was easier to place hand in coat pocket - Physiotherapist/trainer at the gym had remarked on improved hand looseness, which also made it more comfortable - Observed that the looseness in his hand reduced during the latter half of the two week period between interventions.

4.4.3 Discussion on the importance of stimulation with movement

This study aimed to establish whether the combination of voluntary movement and stimulation was key to improvements observed during earlier studies, or if stimulation provided during the rest period between reaching and grasping movements would be equally effective. It has been shown that on average both interventions led to an increase in ARAT score (Figure 4-12), and although only changes in ‘stimulation with movement’ were statistically significant, the small sample size means that this result should be interpreted with caution. ‘Stimulation with movement’ also appeared to have a greater carry-over effect, but this was largely caused by

one individual, and the difference between the two interventions at this time point was not statistically significant. A larger sample will be required to test for any wider trends.

While the average improvement in ARAT score was small, and well below the MCID (≥ 6) [120], the significant improvement observed when data from both interventions are combined (Figure 4-13) is contrary to the idea of a ‘critical window’ for chronic stroke survivors [27]. This result suggests that in some cases, interventions may lead to at least modest short-term improvements for chronic stroke survivors. Although, the small sample size, diversity in starting impairment and other confounders such as Botulinum toxin injections, make it difficult to draw any stronger conclusions from the quantitative data in this study.

Nevertheless, a known challenge in rehabilitation is participant engagement, and despite generally positive qualitative feedback across both interventions (Table 4-4, Figure 4-14 - Panel A), participants reported a strong preference for completing the task with stimulation concurrent with movement (Figure 4-14 - Panel B). Importantly, this might lead to greater participation and subsequent increases in intensity of training. However, whether the modest improvements reported here would translate into continued use in the home or clinical setting is unknown.

In the context of the findings of the extended study reported above, the intervention period for this study appears to have been too short, and the combination of the follow-up period and baseline period prior to the second intervention is problematic for analysis. If this study is to be replicated on a larger scale, a longer training and follow-up period, and a stricter inclusion / exclusion criteria based on impairment levels and other on-going therapies should be employed. Furthermore, as qualitative feedback suggested an improvement in hand and arm looseness, additional assessments such as the Modified Ashworth Scale [131] and, the previously described Fugl Meyer, may be informative.

4.5 Analysis of combined data from the above studies to assess changes observed in a larger sub-population of stroke survivors

4.5.1 Methods

Following the completion of the studies described above, the opportunity was taken to combine data from all studies with stroke participants, to compare the change in ARAT score after two weeks of training with the device to the score recorded immediately prior to the intervention. For participants who completed more than one study, only the first intervention completed was

included, and only data from the ‘stimulation with movement’ intervention (i.e. not ‘stimulation during rest’) was used. Participants were divided into three groups based on their ARAT score immediately before the intervention: ‘<10’, ‘10 to 35’ and ‘>35’. The null hypothesis was that there would be no significant difference between the changes in ARAT score observed for these groups.

Two participants who were assessed as having a maximum score of 57 by the independent blinded assessor, and therefore excluded from the feasibility study (see Section 4.2.2), were included. For reference, the original assessor scored them to both to have increases of 1, whilst the blinded assessor showed no change in score (i.e. 57), which is the value used for this analysis. Also included is participant #4 from the feasibility study who was excluded for having an incomplete dataset, but had completed assessments at both of these time points. Non-parametric statistical testing was carried out using IBM SPSS 24.

4.5.2 Results of the combined analysis

Figure 4-15 shows the average change in ARAT score for each group with the outcome of statistical testing. A statistically significant difference was found between the ‘10 to 35’ and ‘>35’ groups (Post-hoc Dunn test, $P=0.002$). The time since stroke was also calculated for each group, but there was no statistically significant difference between the groups (Kruskall-Wallis test, $\chi^2(2) = 2.665$, $P=0.264$). Furthermore, change in ARAT score was correlated with time since stroke, but no significant correlation was found (Spearman Correlation $\rho=0.132$, $P=0.667$).

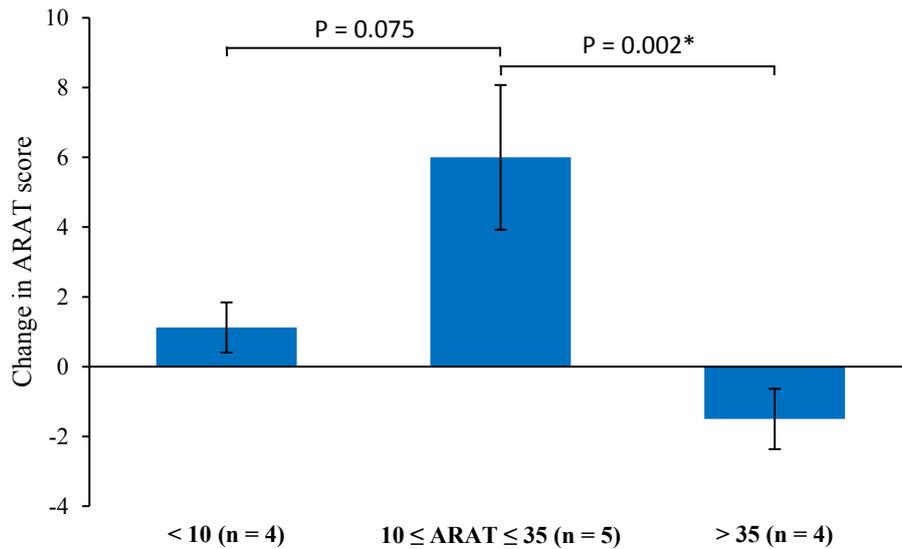


Figure 4-15: The average change in ARAT score following 2 weeks of training with participants grouped by initial ARAT score

A Kruskal-Wallis test found significant differences between the groups ($\chi^2(2) = 9.5, P = 0.009$). Post-hoc tests (Dunn test) found a significant difference between the '10 to 35' and '>35' groups ($P = 0.002$) following a Bonferroni correction for multiple comparisons ($P_{sig} < 0.017$). P values for comparisons between '<10' and '10 to 35', and '<10' and '>35', were 0.075 and 0.228 respectively.

4.5.3 Discussion of combined analysis

This combined analysis across all studies with stroke survivors supports the idea of an optimum impairment level for recruitment based on the ARAT score (Figure 4-15). Improvements appear to be greatest for participants with an initial ARAT score between 10 and 35. Another variable, time since stroke, was also considered, but not found to be significant. However, a larger sample size would be required to further support this finding, and a sub-group analysis of stroke type and location would also be desirable. Furthermore, as discussed earlier, different assessments (e.g. Fugl Meyer) may be sensitive to different types of change in function, and may provide insights missed at the extremities of the ARAT scale.

4.6 Conclusions

Selected participants with chronic stroke were able to use the device, gave generally positive qualitative feedback and in some cases, showed modest improvements on standard functional assessments following a short intervention.

It was shown that when present, these improvements may accumulate with longer interventions and can be captured by a range of functional assessments.

It was not clear whether stimulation delivered with movement led to better outcomes than stimulation applied during the rest periods between voluntary movements, however, participants reported a preference for receiving stimulation with movement.

The intervention may be best suited to stroke survivors with an initial Action Research Arm Test (ARAT) score between 10 and 35. However, a larger sample is required to assess whether other measures (e.g. Fugl Meyer) are better suited to capturing improvements for participants that fall outside this group.

Chapter 5

Investigations into the mechanism of action of the novel device in healthy able-bodied participants

Aim:

- To understand of how the device developed in this thesis might act upon the motor system in healthy able-bodied participants and subsequently, investigate how it might be optimised.

Objectives:

- Following a single session using the device, measure changes in the motor system using non-invasive transcranial magnetic stimulation (TMS) and use this result to elucidate possible mechanisms of action for the intervention
 - Develop and test an optimised intervention, and discuss how this may be beneficial for upper limb rehabilitation following stroke and spinal cord injury (SCI).
-

Acknowledgements / contributions: The dataset presented in this chapter was previously reported in Colin Wan's MRes thesis. Alongside Andrew Jackson, I supervised Colin during his MRes project. Colin was responsible for recruitment and conducting experiments. He also contributed to the study design, and completed his own analysis, discussion and conclusions, which are available in his MRes thesis. I initiated the project, prepared all the experiment and analysis scripts, and completed the analysis and discussion presented in the following chapter. Many thanks to Stuart Baker who advised on the design of the protocol, and Mark Baker for proof-reading this chapter.

5.1 Introduction

Paired associative stimulation (PAS) protocols typically deliver low frequency trains of precisely timed pairs of stimuli to the brain and peripheral nervous system [94, 132]. They have been demonstrated to induce neural plasticity through long-term potentiation (LTP) and long-term depression (LTD) mechanisms [133].

Researchers have shown that inferred endogenous brain activity can be substituted for direct stimulation of the brain [105, 132, 134], and that when paired with voluntary effort, high frequency trains of peripheral stimulation, such as those delivered by functional electrical stimulation (FES), can lead to changes in cortical-spinal excitability [74, 115, 135, 136], which is used as a measure of associative plasticity. Cortical-spinal excitability can be measured using transcranial magnetic stimulation (TMS) to elicit a motor evoked potential (MEP) in the target muscle. The size of the MEP, which can be quantified either by its amplitude or area, reflects the overall excitability of the motor cortex, nerve roots, corticospinal tract and peripheral motor pathways [42].

Earlier in this thesis, it was noted that the timing between the cues (auditory and visual) and the onset of the stimulation had not been optimised. That is, the stimulation is triggered at the same time as the cues, and therefore the time for the brain to process the cue (i.e. the reaction time) and for the signal to be conducted to the muscle, are not accounted for. Paired associative stimulation (PAS) protocols have shown that precise timing between individual stimuli may be important for plasticity effects [96, 105, 137]. It has been suggested that pairing peripheral and descending stimuli can influence voluntary output by acting on corticospinal-motoneuronal synapses located in the spinal cord [113]. In this chapter, the temporal relationship between the cues, inferred brain activity and FES was investigated using the four different conditions, as shown in Figure 5-1: ‘stimulation with movement’, ‘no stimulation’, ‘stimulation during rest’, and ‘delayed stimulation’.

These conditions were split into three studies, with the aim of developing a better understanding of possible plasticity mechanisms, and to provide data against which refined interventions could be compared. It was hypothesised that stimulation concurrent with voluntary cortical activity (‘stimulation with movement’) would lead to a sustained facilitation of cortical-spinal excitability in the stimulated muscles (i.e. Extensor Digitorum Communis (EDC)), compared to either no stimulation (Study 1) or stimulation delivered during the rest period between trials (Study 2). In Study 3, stimulation was delayed relative to the cue in an attempt to converge the

arrival of descending voluntary commands from the cortex with peripheral stimulation (i.e. FES) in the spinal cord. It was hypothesised that this convergence in the spinal cord would lead to increased cortical-spinal excitability and therefore greater drive to the stimulated muscle (i.e. EDC).

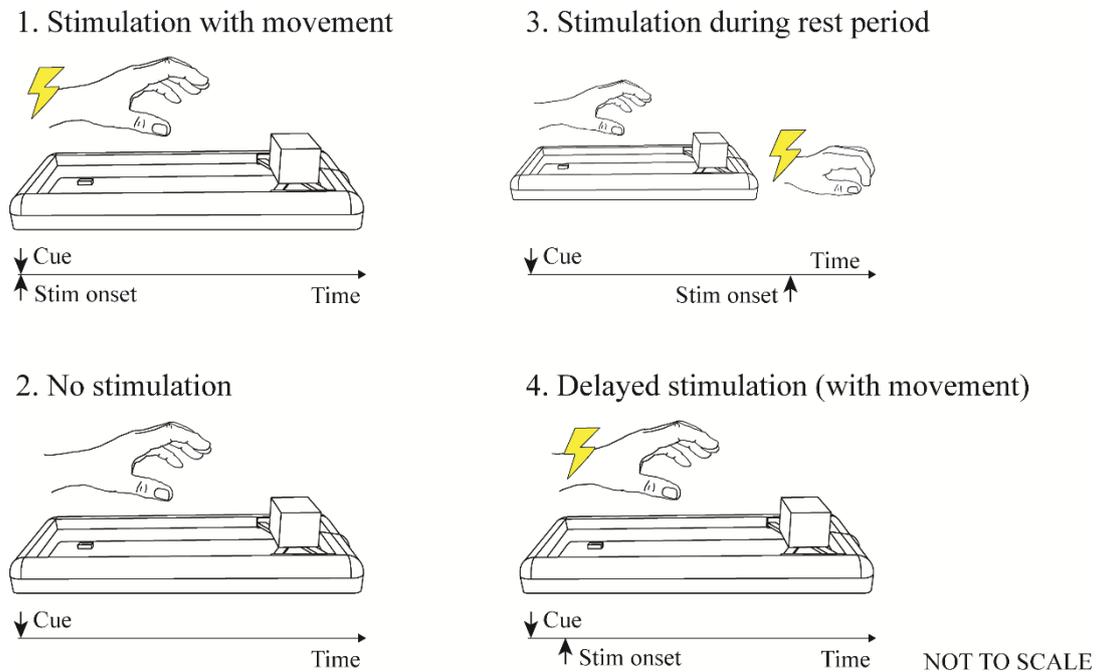


Figure 5-1: An overview of the reaching phase of the task for the four conditions used in this study
 (1) Stimulation was delivered as previously described in the preceding chapters, i.e. stimulation was triggered at the same time as the cue was delivered. For clarity, only the reaching phase of the task is shown here, but a cue and stimulation were also delivered in a similar manner for the release phase of the task. (2) The task was completed without any stimulation. (3) The task was completed without any stimulation, but stimulation was delivered during the rest period between trials. (4) Stimulation was delivered as previously described with movement, but the stimulation onset was delayed to account for reaction and conduction times.

5.2 Methods

5.2.1 Participants

Healthy able-bodied participants were recruited at the Institute of Neuroscience, Newcastle University (UK). Recruitment was subject to the following exclusion criteria: any history of neurological disease (e.g. epilepsy), implanted devices (e.g. a pacemaker), skin sensitivity, a high-level spinal cord injury, a cancerous tumour in the arm or shoulder, a fracture in the arm or shoulder, a metallic implant in the arm or head, or pregnancy. The study received ethical approval from the local ethics committee at Newcastle University, and all participants gave written informed consent. Participants received reimbursement for their time / travel expenses.

5.2.2 Measurement of corticospinal excitability with Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a non-invasive technique that can be used to investigate corticospinal excitability [42-44]. Magnetic stimuli were delivered using a Magstim BiStim² (The Magstim Company Ltd) with a Magstim Double 70mm Coil (D70² Coil). To record motor evoked potentials (MEPs) bipolar surface electromyography (EMG) (Natus Disposable Snap Electrodes 33x22cm) was used to record from the extensor digitorum communis (EDC) and flexor digitorum superficialis (FDS) on the dominant side (unless otherwise requested by the participant) and a reference electrode was placed on the back of the wrist. EMG data were collected using a Digitimer D360 amplifier, CED MICRO2 1401 with ADC12 Expansion data acquisition interface (Cambridge Electronic Design Ltd) and Spike2 software (Cambridge Electronic Design Ltd). The set-up is shown in Figure 5-3.

Participants were seated at a table, with their arms at rest on a cushion placed in front of them. Head and coil position were tracked using a TMS neuronavigation system (Brainsight, Rogue Research). The coil was positioned over the motor cortex at 45° to the midline and tangential to the skull (known as the posterior-anterior (PA) position [138]), and a ‘hotspot’ was located for the EDC muscle. Motor threshold, defined as the lowest intensity required to elicit a MEP response greater than 50µV peak-to-peak more than 50% of the time [42], was found for the EDC and the stimulator was subsequently set at 120% of this value.

Twenty-five MEPs were recorded before, immediately after, 15 minutes after and 30 minutes after the intervention (200 repetitions). This is shown in Figure 5-2. TMS was delivered with an inter-stimulus interval (ISI) of 4-6s.

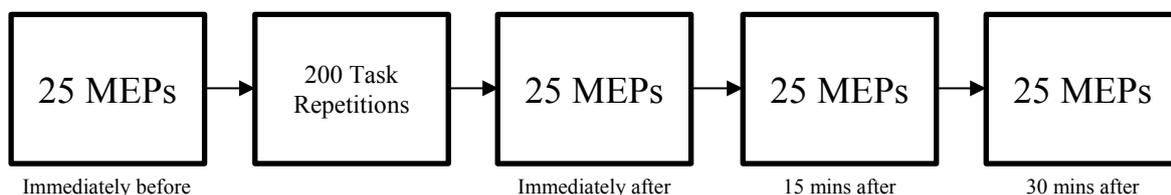


Figure 5-2: An overview of the protocol used throughout this chapter

Motor evoked potentials (MEPs) were recorded at set points before and after the intervention to investigate changes in corticospinal excitability.

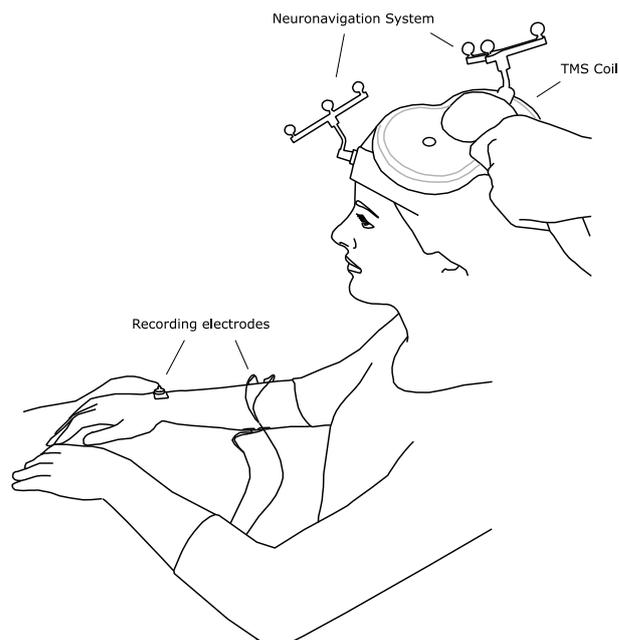


Figure 5-3: The TMS set-up used in this study

Bipolar EMG was recorded from the EDC and FDS muscles, with a reference electrode placed on the back of the wrist. The coil was placed in posterior-anterior (PA) position [138] on the contralateral side to the recorded muscles. The participant's arms were placed on a cushion on a table and maintained at rest. The subject tracker and coil tracker for the neuronavigation system can be seen positioned on the TMS coil and on the participant's forehead.

5.2.3 Study 1 - A comparison of changes in corticospinal excitability induced by completing the task with and without stimulation

This study investigated the difference in cortical excitability induced by completing 200 repetitions of the intervention with ('stimulation with movement') and without ('no stimulation') FES stimulation. Participants visited the lab twice with a seven day interval between visits, and at approximately the same time of day. They were allocated into two groups: 'with stimulation first' and 'without stimulation first', in a pseudo-random manner, i.e. they were alternately allocated into these groups based on the order they were recruited. The protocol is shown in Figure 5-4.

Stimulation was set-up as previously described (see Chapter 3) and delivered to the forearm to assist finger, hand and wrist extension only. First, the intensity (current and pulse width) required to elicit a twitch in the index finger was found, and then the pulse-width increased to approximately 1.5 times this value. It was explained to participants that the stimulation was to enhance or assist their voluntary movements, not to override them, and that they should work with the stimulation to complete the task.

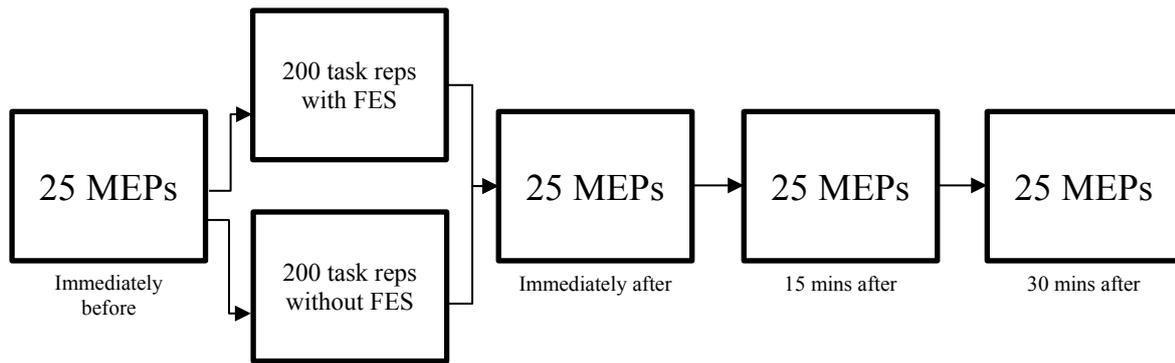


Figure 5-4: The protocol used to compare changes in corticospinal excitability with and without FES delivered during the intervention

Participants completed both interventions, at least 7 days apart, and where possible, at the same time of day.

5.2.4 Study 2 - Changes in corticospinal excitability induced by stimulation delivered during the rest period between trials

In this second study, participants received stimulation during the rest period between trials and not during the movement phase of the task. This meant that voluntary effort and stimulation were unpaired. Stimulation was set-up as above, delivering stimuli to the extensors muscles only, and participants were instructed to remain passive during stimulation. The intervention protocol is shown in Figure 5-5.

Stimulation was delivered in two bursts to replicate the reaching and releasing phases of the task. The time stimulated was based on pilot data collected from five healthy able-bodied participants who completed 50 repetitions of the task without stimulation. Timings were (mean \pm SE): reaching phase 1.0 ± 0.1 s and releasing phase 0.9 ± 0.1 s.

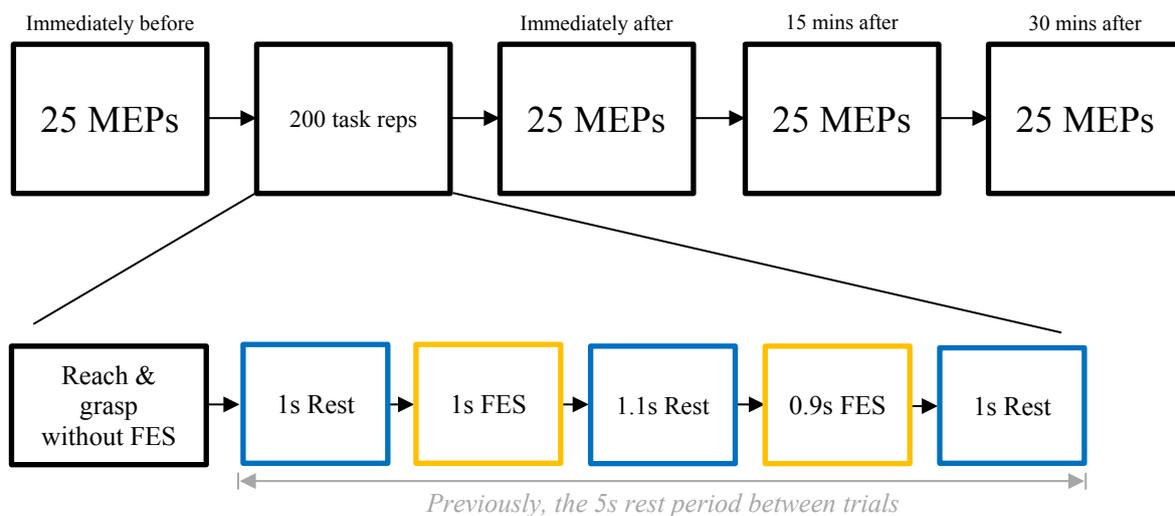


Figure 5-5: The protocol used to investigate changes in corticospinal excitability induced by stimulation delivered in two bursts during the rest period between trials

5.2.5 Study 3 – Investigating an optimised stimulation protocol designed to facilitate corticospinal excitability following the intervention

In this third study, the onset of the FES was timed to theoretically converge with the arrival of voluntary commands from the cortex in the spinal cord. The timing was calculated using pilot data from 10 healthy able-bodied controls who completed 50 repetitions of the task whilst EMG was recorded from the EDC muscle. The time from the cue to muscle activity onset, defined as five standard deviations above the baseline mean (found using a 100ms period before cue), was calculated in Spike2 software using DC offset and rectified data. The typical EDC reaction time was found to be $151 \pm 1\text{ms}$ (mean \pm SE) and $142 \pm 16\text{ms}$ for the ‘reach and grasp’ and ‘release’ phases of the task respectively. An estimate of the peripheral motor conduction time (PMCT) for EDC (9.3ms [139]) was then subtracted twice from these values, to give a delay between the cue and stimulation of 133 and 123ms for the two phases of the task.

It should be noted that these timings are based on a group average, and therefore only an approximation of optimal timing. Furthermore, there are potential delays between the control signal sent to the stimulator and actual delivery of stimulation, although pilot studies suggested this was minimal. However, depending on the stimulator design, this could be up to +25ms for a 40Hz stimulation train.

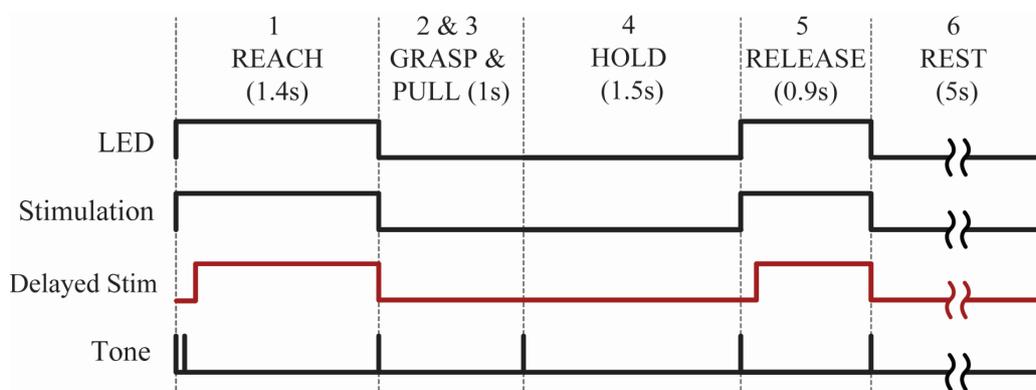


Figure 5-6: The ‘delayed stimulation’ condition

A comparison of the stimulation previously used in the ‘stimulation with movement’ condition (as used in Study 1 above) and the ‘delayed stimulation’ condition (red) used in this study. The stimulation onset was delayed relative to the cue to try to converge ascending and descending signals in the spinal cord. Stimulation was delivered to the extensor muscles only, to facilitate hand, finger and wrist extension.

5.2.6 Data Analysis

To ensure the TMS stimulation threshold used for the EDC muscle was also sufficient for the FDS muscle, responses were visually inspected offline to ensure MEPs were consistently

evoked in both the EDC and FDS muscles, with those not meeting this criteria removed. These occurrences are noted in the results section.

To investigate changes in MEP size (area) pre- and post-intervention, data were imported into MATLAB (The MathWorks Inc.) and a ~58ms window extracted following each TMS stimulus, with the stimulus artefact avoided. Each window was zero-meaned and then rectified, before being integrated to find the MEP area. The mean MEP area was then found for each session for each participant, and presented as a percentage of the pre-intervention MEP size. This showed whether the average MEP size had been either facilitated, suppressed or if no change had occurred following the intervention. This result was then averaged across participants to find the group average change in MEP size post-intervention relative to the pre-intervention response.

Baseline EMG immediately prior to each TMS stimulus was also analysed to see if the intervention would affect baseline activity levels. MEP responses are affected by changes in baseline EMG [140]. Furthermore, it would allow anomalies to be identified, for example an anonymously large one-off increase in baseline activity. To this end, a 50ms window was extracted prior to each TMS stimulus and the area found as previously described for MEPs. The results were averaged across trials and individuals to look for group-wide changes.

Statistical analysis was completed in MATLAB. Normality was tested for using a Lilliefors test on datasets with sample sizes below 20 [141, 142]. All tested datasets were found to be normally distributed except for the FDS muscle, 30 minutes post-intervention in the ‘no stimulation’ condition and the EDC muscle in the ‘stimulation during rest’ condition 15 minutes post-intervention. In light of the remainder of the dataset, and with sample sizes approaching recommended lower limits for t-tests [141, 142], paired and unpaired t-tests were applied to compare pre- and post-intervention, between muscles (EDC and FDS) and between conditions (e.g. ‘stimulation with movement’ vs. ‘no stimulation’). The null hypotheses for statistical testing of MEPs were: (1) there was no significant difference between the size of the pre- and post- intervention MEPs (0, 15 and 30 mins) for a particular muscle and intervention (completed at a group and individual level), (2) there was no significant difference in the percentage change in MEP size between muscles at a particular time-point and intervention (group level only), and (3) that there was no significant difference in the percentage change in MEP size for particular muscle and time point between interventions (group level only). A null hypothesis equivalent to (1) was applied to the baseline data.

5.3 Results

5.3.1 Participants

Fifteen healthy able-bodied volunteers were recruited to Study 1 – ‘stimulation with movement’ vs. ‘no stimulation’ (23 ± 0.7 years old (mean \pm SE), 6 female), 15 were recruited for Study 2 – ‘stimulation during rest’ (23 ± 0.5 years old, 10 female) and 10 were recruited for Study 3 – ‘delayed stimulation’ (24 ± 0.8 , 5 female). Eight of the participants in Study 1 also completed Study 2, and 4 also completed Study 3. Seven participants from Study 2, also completed Study 3. Two participants completed all three studies. In these instances, the studies were separated by at least 7 days. Stimulation current values ranged from 22.5 to 29mA, and pulse widths from 110 to 360 μ s.

5.3.2 Study 1 – Change in corticospinal excitability in ‘stimulation with movement’ vs. ‘no stimulation’

All 15 participants completed the study, however one participant reported illness prior to their second session, leading to notably different responses, and therefore their dataset was excluded from the analysis. All participants received stimulation to their dominant side, with one exception who had a pre-existing injury on this side.

This study investigated the differences between completing the task with and without stimulation. For the flexor (FDS) muscle (Figure 5-7), both the ‘stimulation with movement’ and ‘no stimulation’ conditions showed significant increases compared to pre-intervention measurements immediately following the intervention ($P=0.008$ and $P=0.038$). The excitability of the extensor (EDC) muscle was significantly reduced from pre-intervention measurements immediately after the intervention in the ‘stimulation with movement’ condition ($P=0.047$). This is in contrast to the extensor muscle following the ‘no stimulation’ condition. Here, excitability increased by 9% immediately after, and although not immediately significant, the increase was significant 30 minutes post-intervention. A comparison between the ‘stimulation with movement’ and ‘no stimulation’ responses in the EDC muscle immediately after the intervention was near significance ($P=0.06$).

Analysis of individual datasets (Figure 5-8 and Figure 5-9) showed some variation between participants, with individual’s exhibiting significant facilitation and suppression in both conditions. However, as reflected in the group data, a bias towards facilitation in both muscles can be seen in the ‘no stimulation’ condition, and the flexor muscle in the ‘stimulation with movement’ condition. Similarly, a large number of individuals (8 out of 14) showed a

suppression of the extensor muscle immediately following the ‘stimulation with movement’ condition.

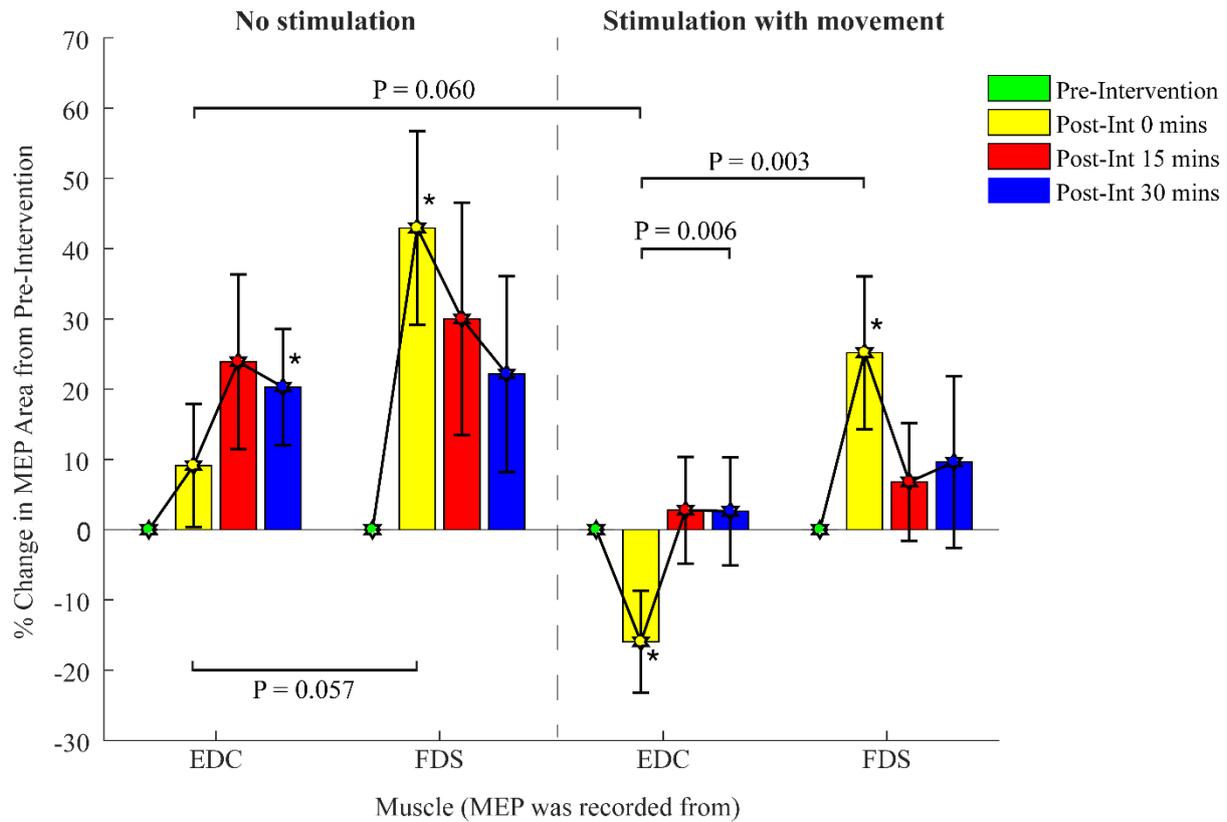


Figure 5-7: Average change in MEP size in the ‘no stimulation’ and ‘stimulation with movement’ conditions following the intervention

The average percentage change in MEP area for the ‘no stimulation’ and ‘stimulation with movement’ conditions measured from the extensor (EDC) and flexor (FDS) muscles (n=14) relative to the pre-intervention measurement. * indicates a significant change (P<0.05) from the pre-intervention value, measured using a paired t-test. Values from left-to-right are 0.032, 0.008, 0.047 and 0.038. Horizontal lines indicate further paired t-tests which were significant, or approaching significance if deemed of particular interest.

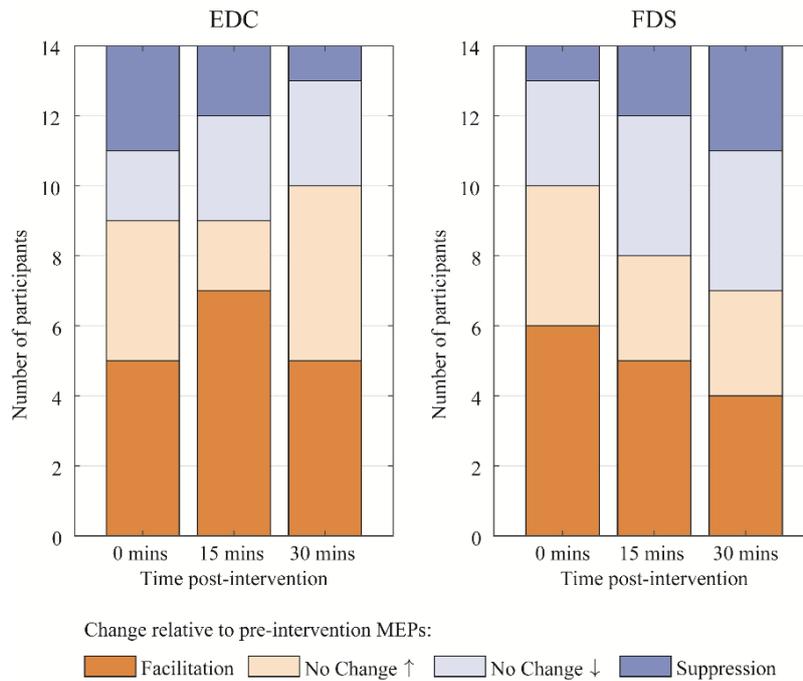


Figure 5-8: Individual changes in MEP size following the ‘no stimulation’ intervention

The number of participants showing significant facilitation, suppression or no change at each post-intervention time point for the ‘no stimulation’ condition. Significance was calculated for each individual using an unpaired t-test to compare the individual MEPs at each post-intervention time point to the pre-intervention MEPs. Significant facilitation and suppression were defined as $P < 0.05$.

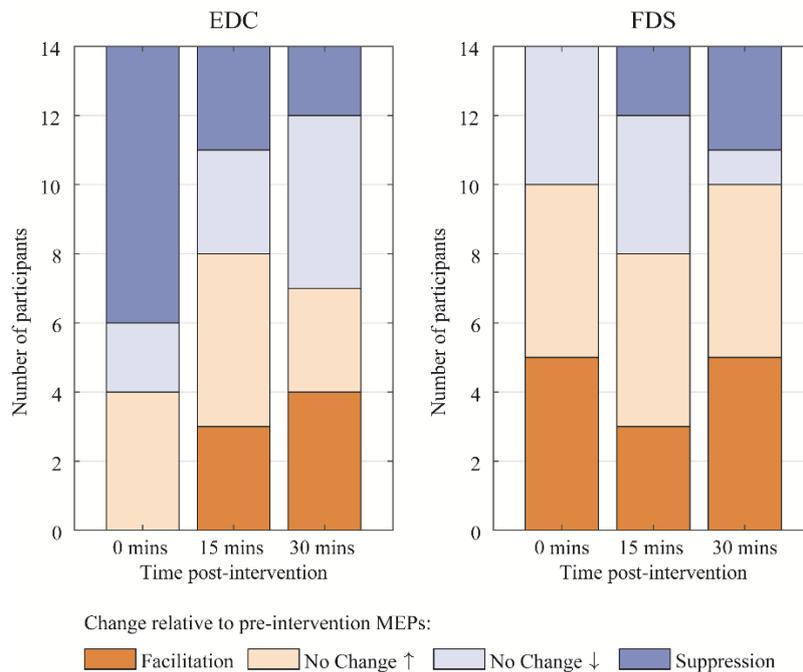


Figure 5-9: Individual changes in MEP size following the ‘stimulation with movement’ intervention

The number of participants showing significant facilitation, suppression or no change at each post-intervention time point for the ‘stimulation with movement’ condition. Significance was calculated for each individual using an unpaired t-test to compare the individual MEPs at each post-intervention time point to the pre-intervention MEPs. Significant facilitation and suppression were defined as $P < 0.05$.

5.3.3 Study 2 - Changes in corticospinal excitability induced by stimulation delivered during the rest period between trials

Fifteen participants completed the study, but participant #12 was excluded due to inadequate MEPs in the FDS (flexor) muscle. Participant #1 showed an anomalously large (approx. 800%) increase in baseline EMG at the ‘post-intervention 0 minutes’ time point and was also excluded. Figure 5-10 shows the group average data from the ‘stimulation during rest’ condition alongside the ‘stimulation with movement’ condition from Study 1. A suppression can be observed in both muscles in the ‘stimulation during rest’ condition, but this is not significant. The analysis of individual data reflects this (Figure 5-11), with just under half (6 / 13) of participants showing a significant suppression in the EDC muscle, and this number is sustained at 15 minutes.

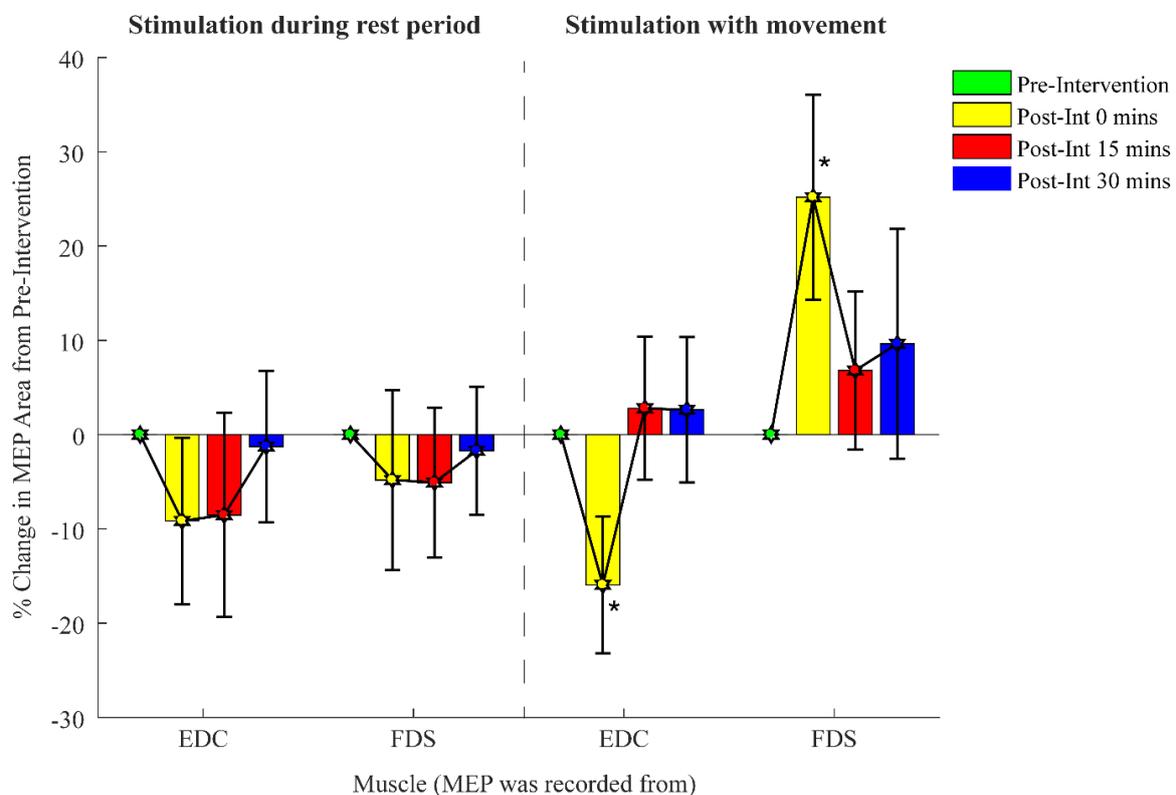


Figure 5-10: Average change in MEP size following the ‘stimulation during rest’ and ‘stimulation with movement’ interventions

Left - The average percentage change in MEP area for the ‘stimulation during rest’ condition ($n=13$) relative to the pre-intervention condition measured from the extensor (EDC) and flexor (FDS) muscles. Right – For comparison, results from ‘stimulation with movement’ as shown in Figure 5-7. There were no significant changes from the pre-intervention MEPs for the ‘stimulation during rest’ condition. Furthermore, there were no significant differences between the two interventions, between muscles, or between post-intervention time points for ‘stimulation during rest’.

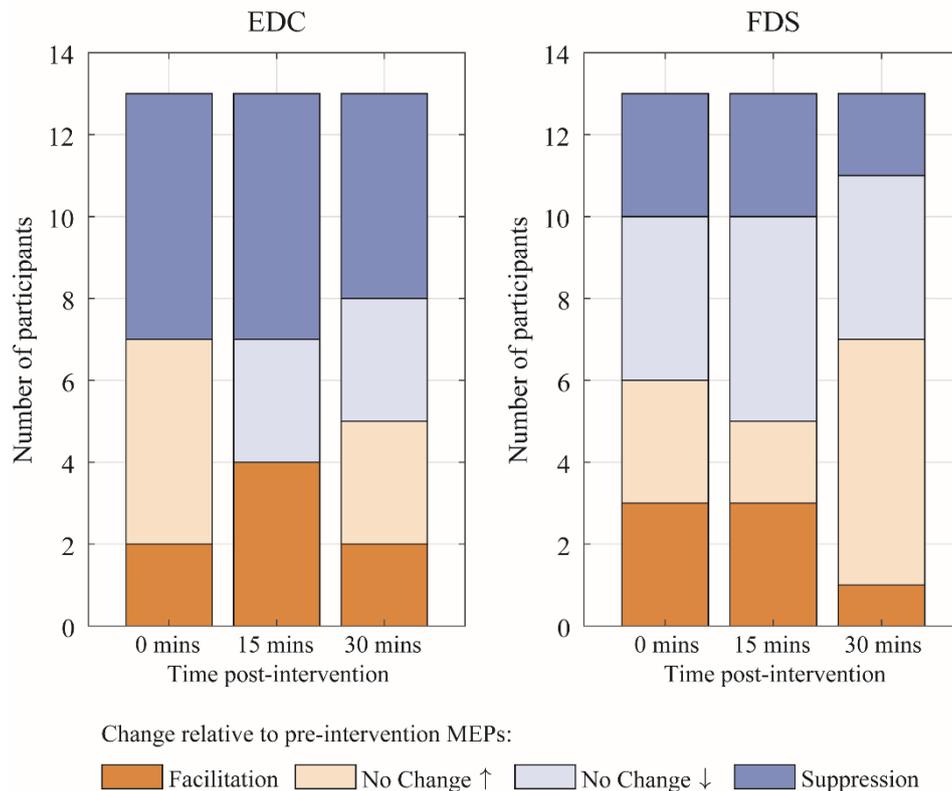


Figure 5-11: Individual changes in MEP size following the ‘stimulation during rest’ intervention
 The number of participants showing significant facilitation, suppression or no change at each post-intervention time point for the stimulation during rest condition. Significance was calculated for each individual using an unpaired t-test to compare the individual MEPs at each post-intervention time point to the pre-intervention MEPs. Significant facilitation and suppression were defined as $P < 0.05$.

5.3.4 Study 3 – Investigating an optimised stimulation protocol designed to facilitate corticospinal excitability following the intervention

Ten participants completed Study 3 which investigated a ‘delayed stimulation’ condition. Participant #7 was excluded as MEPs were not consistently evoked in the FDS (flexor) muscle. Figure 5-12 shows the group average data from this condition alongside the ‘stimulation with movement’ data from Study 1. A large facilitation can be observed for the FDS muscle, which remains significant at 30 minutes, furthermore, this is statistically significant when compared with the facilitation observed immediately post-intervention in the ‘stimulation with movement’ condition. In contrast, there is very little change from baseline for the EDC muscle. Analysis of individual data (see Figure 5-13) emphasises this result, with a mix of suppression and facilitation for the EDC muscle, but importantly, no significant suppression at any time point for the FDS muscle.

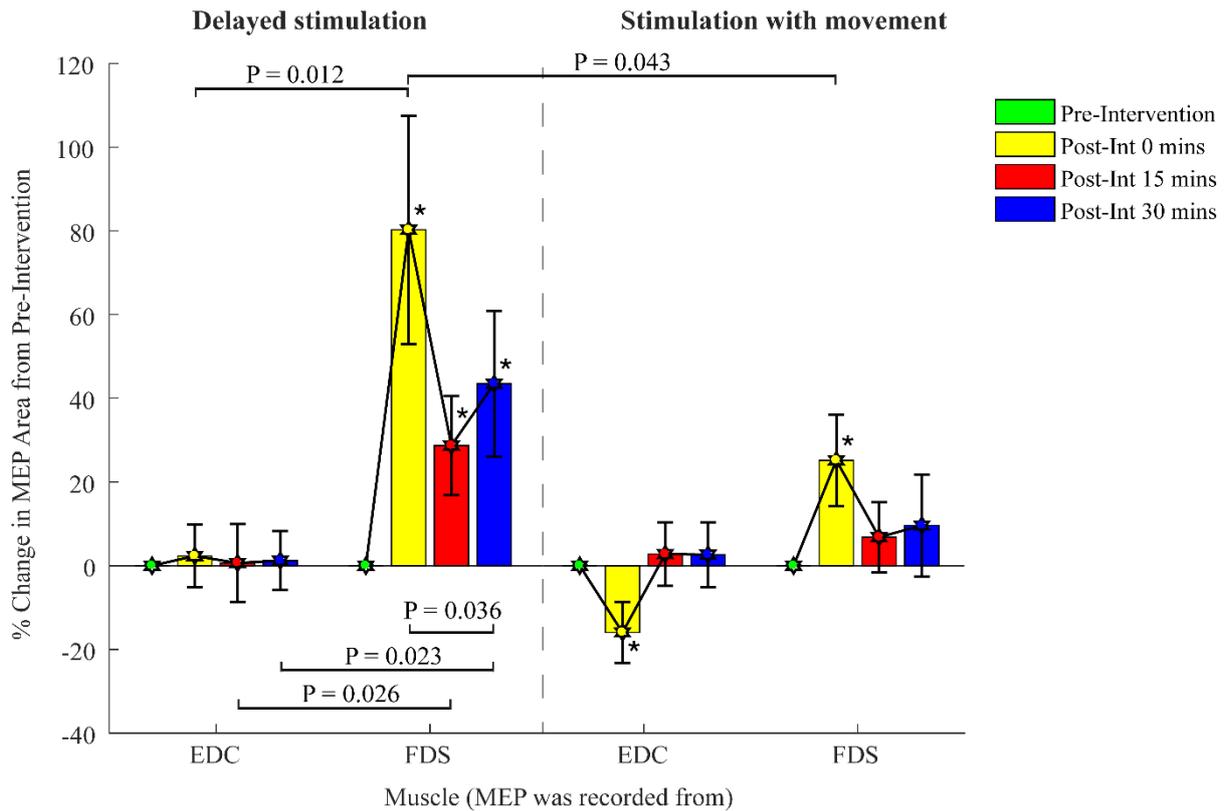


Figure 5-12: Average change in MEP size following the 'delayed stimulation' and 'stimulation with movement' interventions

Left - The average percentage change in MEP area for the 'delayed stimulation' condition (n=9) relative to the pre-intervention condition measured from the extensor and flexor muscles. Right - For comparison, results from 'stimulation with movement' (n=14) as shown in Figure 5-7. A paired t-test was used to compare pre- and post- intervention measures, significant (P<0.05) results are indicated with *. Values from left-to-right are 0.019, 0.042, 0.037, 0.047 and 0.038. Horizontal lines indicate further paired and unpaired t-tests which were found to be significant.

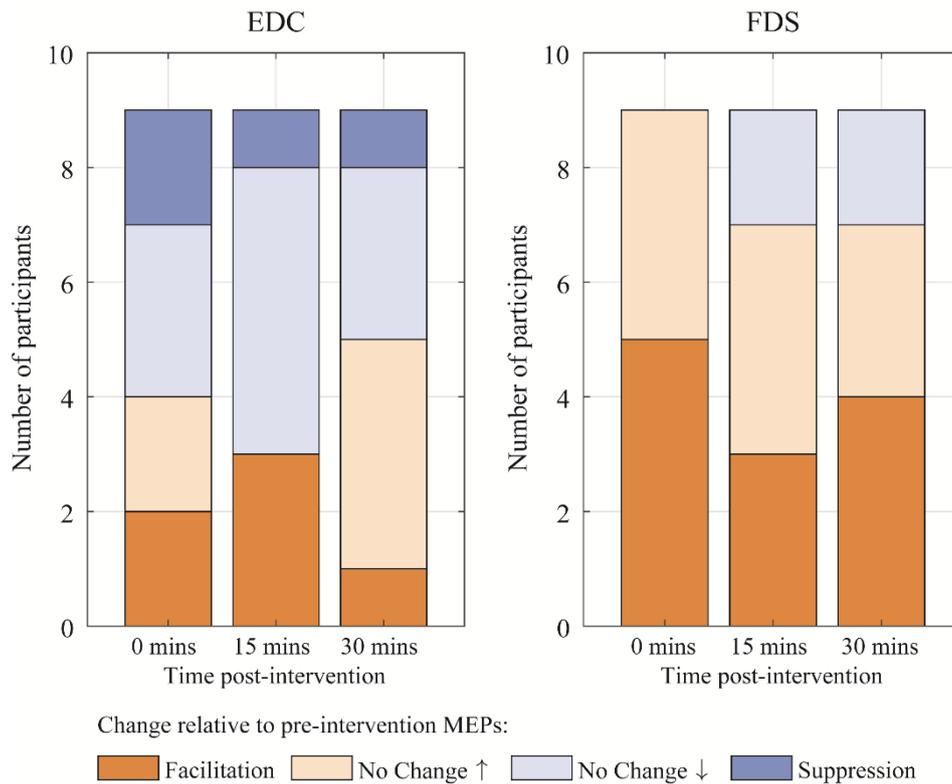


Figure 5-13: Individual change in MEP size following the 'delayed stimulation' intervention

The number of participants showing significant facilitation, suppression or no change at each post-intervention time point for the delayed stimulation condition. Significance was calculated for each individual using an unpaired t-test to compare the individual MEPs at each post-intervention time point to the pre-intervention MEPs. Significant facilitation and suppression were defined as $P < 0.05$.

5.3.5 Investigating changes in baseline EMG across all conditions

Baseline EMG immediately prior to each TMS stimulus was investigated to look for possible confounders and for any group-wide changes that may have been brought-about by the intervention. There were no significant changes in baseline EMG for the 'stimulation with movement' and 'no stimulation' conditions (Figure 5-14). However, the 'delayed stimulation' condition showed significant increases in baseline EMG in both extensors and flexors after 30 minutes (Figure 5-15). The 'stimulation during rest' condition showed a significant decrease in baseline flexor activity across all time points (Figure 5-15). As the baseline EMG is much smaller than the MEP size, it is not anticipated that the changes measured in MEP size (reported above) are simply due to a fluctuating contributions from baseline activity.

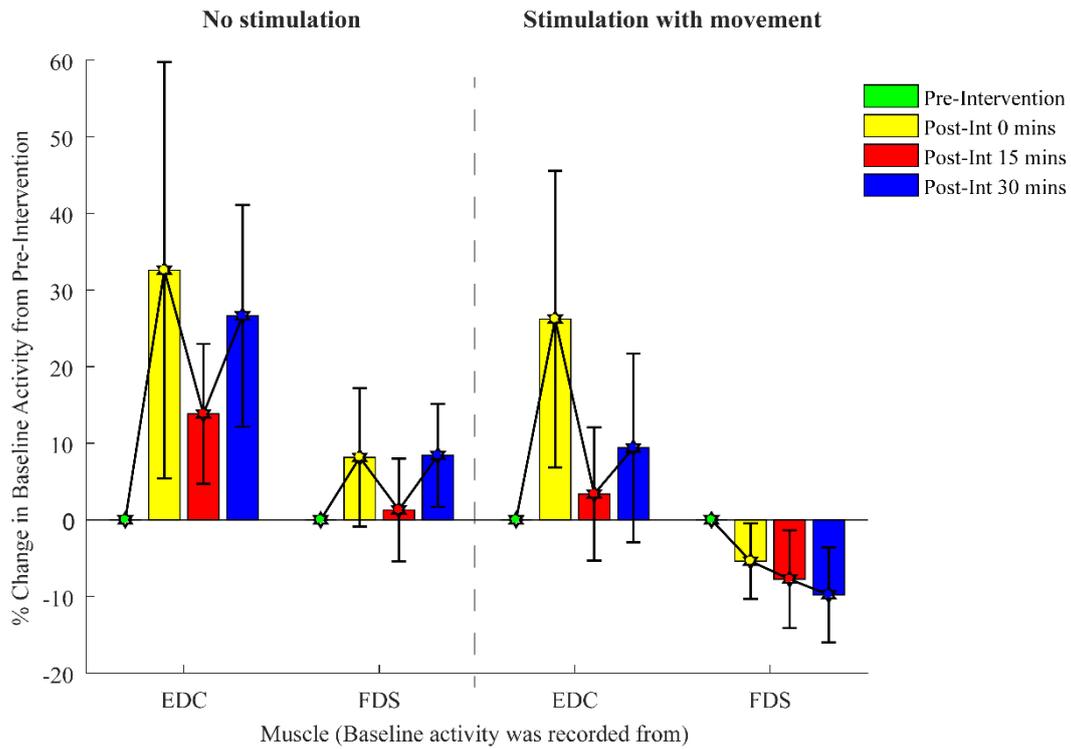


Figure 5-14: The percentage change of baseline EMG activity relative to pre-intervention values during the 'no stimulation' and 'stimulation with movement' conditions. There were no significant changes from baseline ($P < 0.05$).

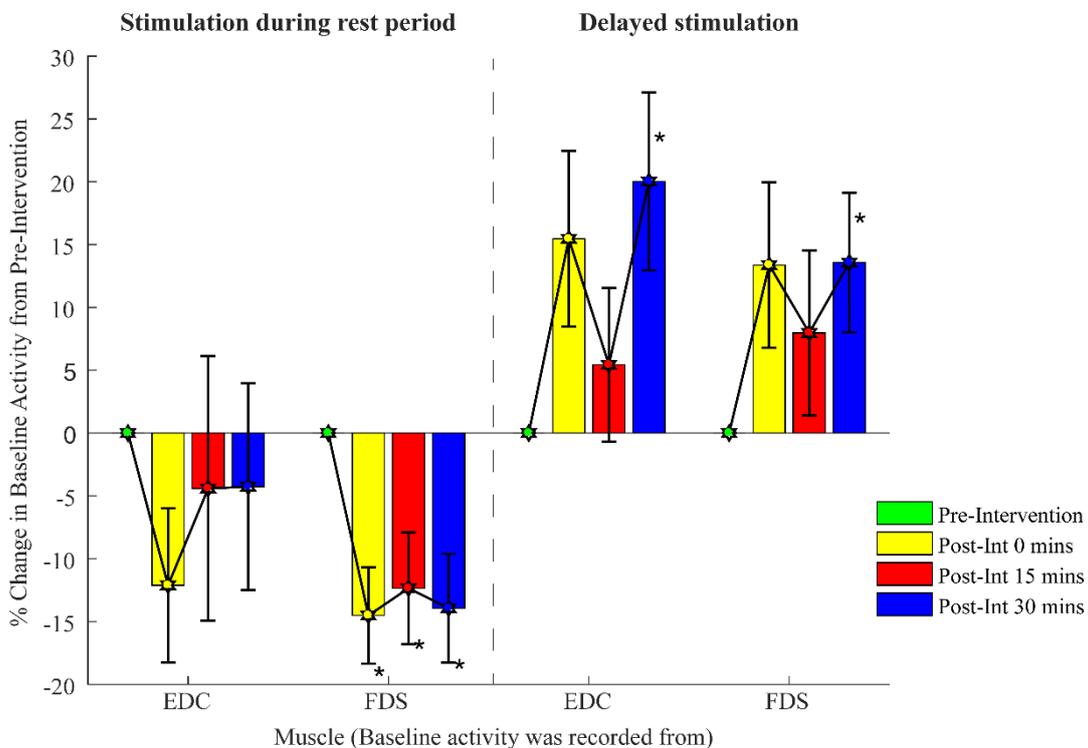


Figure 5-15: The percentage change of baseline EMG activity relative to pre-intervention values during the 'delayed stimulation' and the 'stimulation during rest period' conditions. * indicates a significant change from pre-intervention, defined as $P < 0.05$, calculated using a paired t-test. Significant values from left to right are 0.022, 0.04, 0.003, 0.017 and 0.007.

5.4 Discussion

5.4.1 Study 1 - A comparison of changes in corticospinal excitability brought about by completing the task with and without stimulation

Facilitation was observed in both extensor (EDC) and flexor (FDS) muscles following the 'no stimulation' condition (Figure 5-7). As it has previously been reported that non-fatiguing exercise can lead to an increase in MEP size [143], this was not an unexpected result. However, the postulated additional facilitation of the extensor muscle when paired with stimulation did not occur. In contrast, a significant suppression was recorded immediately after the intervention (Figure 5-7).

This could have been caused by FES induced muscle fatigue, and is supported by the observation that on average suppression did not occur in the unstimulated muscle. FES is known to cause fatigue through its mode of action and reverse recruitment of muscle fibres [65]. However, although not specifically asked, participants did not report significant fatigue following the intervention [144], but participants may not report lower levels of discomfort / tiredness. Future studies could test for muscle fatigue by testing a participant's maximal voluntary contraction, or by using physiological measures such as the maximal compound muscle action potential (M_{max}) and twitch interpolation [145].

A suppression of MEP size following fatiguing exercise has been reported to last for eight minutes following wrist extensions of 90s or more [143]. This eight minute time-course would be in line with the results observed here, but only if the two exercises can be considered comparable. As the mean-time to fatigue in the wrist extension study was 130s, it seems unlikely this study caused such high levels of fatigue. Other studies investigating corticospinal excitability following FES do not appear to have induced a suppression [135, 146], and it is not clear why this task would bring about greater levels of fatigue. Nevertheless, it was anticipated that if caused by fatigue, the effect would also be seen in the subsequent conditions ('stimulation during rest' and 'delayed stimulation') where similar levels of stimulation were delivered.

Interestingly, Kotan and colleagues [147], who also reported a reduction in corticomotor excitability following fatiguing electrical stimulation, believed that the reduction was caused by intracortical inhibitory mechanisms. This suggests that even if the effect is caused by fatigue, this type of training is activating the cortex, which could lead to longer term changes in motor function.

An alternative explanation is that as the FES is activating the muscle required for completing the task, the intervention leads to a reduction in voluntary drive to that muscle and subsequently, a decrease in corticospinal excitability immediately following the intervention. The observed suppression could also be explained by the importance of the order of pre- and post-synaptic activity in Hebbian plasticity. Paired associative stimulation (PAS) protocols have shown that if nerve stimulation precedes cortical stimulation (TMS) then a sustained suppression of the MEP is recorded, indicating long term depression (LTD) of synaptic activity [148]. However, the evidence from studies using trains of stimuli is more complex. Here, peripheral nerve stimulation (PNS) prior to TMS has also been reported to increase MEP amplitude [149, 150]. Furthermore, the suppression is not sustained in this dataset, which is opposite to that observed in PAS studies.

Similarities between the ‘stimulation with movement’ and ‘no stimulation’ interventions are not necessarily undesirable. The facilitation of the FDS muscle in both interventions, demonstrates that, in this muscle at least, FES combined with movement can lead to similar changes in cortical excitability as exercise alone, suggesting that this may be a useful substitute in situations where movement alone is not possible.

5.4.2 Study 2 - Changes in corticospinal excitability induced by stimulation delivered during the rest period between trials

This study aimed to elucidate whether concurrent FES stimulation and movement were required to elicit changes in corticospinal excitability, or if similar changes would be observed when the individual components (movement and FES) were delivered separately, i.e. stimulation delivered during the rest period between voluntary movements.

At a group level, no significant changes from the pre-intervention measurements were found. Responses in the EDC appeared to decrease, but this was not significant, and notably responses did not appear to immediately return to pre-intervention levels as observed in the ‘stimulation with movement’ condition. As previously discussed, this may be caused by fatigue, but the lack of significance and different time-course casts some doubt on this hypothesis. Similarly, based on this dataset, it is difficult to support or refute the influence of the temporal order of pre- and post- synaptic activity on changes to cortical excitability, or a reduction in voluntary effort.

The elimination of any facilitation of the FDS muscle is remarkable, and unexpected. The flexor muscle does not receive any stimulation, and would therefore be expected to respond in

a similar manner to the ‘no stimulation’ condition. This result may in part be explained by the significant reduction in baseline EMG which is maintained for 30 minutes (Figure 5-15). This has implications for rehabilitation, as a reduction in baseline flexor excitability may be advantageous with regards to spasticity, as it could indicate a reduction in resting muscle tone.

It is therefore suggested, that although there are no significant differences between the MEPs in the ‘stimulation with movement’ and ‘stimulation during rest’ conditions, the elimination of significant FDS facilitation, as well as changes in baseline EMG, are indications of different mechanisms of action for the two conditions.

5.4.3 Study 3 – Investigating an optimised stimulation protocol designed to facilitate corticospinal excitability following the intervention

This condition was designed to optimise the timing of the descending and ascending commands to maximise Hebbian plasticity by convergence of signals in the spinal cord. Notably, in the group-wide data (Figure 5-12) a facilitation of pre-intervention MEP was not found for the EDC muscle, but a large facilitation of the FDS muscle was observed. Furthermore, this facilitation was significantly greater than that observed in the ‘stimulation with movement’ condition and was significant compared to pre-intervention levels, and the EDC muscle, for 30 minutes. Furthermore, no participants showed a significant suppression in this condition (Figure 5-13). Baseline EMG was found to be significantly greater than pre-intervention at 30 minutes (Figure 5-15), and therefore an increase in the overall excitability of the system may partially explain the significant increase in flexor response. It is also worth noting that different groups of participants completed Study 1, Study 2 and Study 3, and therefore the observed effects may reflect variation amongst individuals, although statistical testing should indicate group-wide effects.

The extensor muscle did not show a decrease in excitability, as previously observed in Study 1, and although in this condition slightly less stimulation is delivered, this result is still contrary to the previously hypothesised muscle fatigue. The result does provide some support for the importance of the temporal order of pre- and post- synaptic activity, but it must be noted that any suppression may be offset by an increase in baseline extensor excitability, which would be anticipated to lead to an increase in MEP size [140].

An interesting comparison can be made between the two stimulation concurrent with movement conditions (‘stimulation with movement’ and ‘delayed stimulation’). They both showed significant differences between the EDC and FDS muscles immediately after the

intervention, demonstrating that when delivered in the manner presented here, stimulation concurrent with movement leads to significant short-term changes in the relative excitability of this muscle pair.

A limitation of the approach presented here is that an average reaction time was used to calculate the stimulation delay. It is clear that this will not provide optimum timing for all participants. Future studies could use the reaction time for each individual, providing personalised stimulation timings. Additionally, a condition in which the stimulation is delivered much later, say 200-300ms after the cue, would be an interesting control condition. In participants with stroke, the reaction time could be calculated using the less impaired arm, or using average data from an aged-matched sample.

It was assumed that plasticity would occur in the spinal cord. However, other researchers who have targeted plasticity in the brainstem, and have timed afferent stimulation to arrive in the brainstem prior to activation of the descending excitatory postsynaptic potential (EPSP) [151]. They argue that this will potentiate the EPSP, leading to an increase in connectivity. It has also been shown that peripheral electrical stimulation co-modulates primary sensory and motor cortex excitability, which suggests that the early afferent input generated by the ‘stimulation with movement’ condition may be better suited to increasing cortical excitability prior to the generation of descending commands [152]. It is evident that further studies are required to elucidate the interaction of ascending and descending signals, enabling informed refinement of stimulation protocols.

Finally, the TMS protocol used stimuli at 120% of the resting threshold for the EDC muscle, however, the FDS muscle was also analysed. It is not known what percentage of resting threshold was used for this muscle, with possible floor and ceiling plateau effects, i.e. stimulation of insufficient magnitude to generate a response, or so great that it leads to a saturation of responses. However, visual inspection ensured adequate responses which should counter any floor effect, and the facilitation observed suggests that a ceiling was not being met.

5.4.4 General discussion

We have provided evidence that stimulation concurrent with movement (‘stimulation with movement’ and ‘delayed stimulation’) leads to a significant increase in the excitability of the flexor (FDS) relative to the extensor (EDC) muscle immediately after the intervention. Furthermore, stimulation delayed to converge with descending commands in the spinal cord (‘delayed stimulation’) led to a significantly greater facilitation of the flexor muscle compared

to stimulation delivered simultaneously with the cue ('stimulation with movement'). This was not the hypothesised outcome, but leads to two salient discussion points: (1) what underlying physiology might have caused this, and (2) how might these changes explain the results observed in earlier studies with stroke survivors and participants with SCI? In this section, we look at the evidence for two possible mechanisms: reduced voluntary effort, and a flexor / extensor bias in the motor system, and then discuss how this might translate to people with neurological conditions such as stroke and SCI.

5.4.4.1 *Reduced voluntary effort*

It is known that voluntary effort can be regulated by the supraspinal factors [145] and it is suggested that the addition of FES may lead to a reduction in this required effort. This may lead to a down regulation of the input from the cortex to the extensor muscle, and subsequently reduced responses to TMS. Furthermore, through reciprocal inhibition, a down-regulation of extensor input from the cortex, could lead to reduced inhibition of the corresponding flexor muscles and subsequently, greater flexor MEPs as observed here.

However, contrary to this hypothesis, the extensor muscle was not suppressed by the 'delayed stimulation' condition (Figure 5-12) and a trend towards suppression was observed in the 'stimulation during rest' condition (Figure 5-10), although changes in baseline EMG may have also affected this (Figure 5-15). In future studies, the reduced voluntary effort hypothesis could be tested by asking participants to generate a particular grip force with feedback before the intervention, and then the same force, without feedback, following the intervention. This would address whether 'stimulation with movement' led to an underestimate of the required force compared to 'no stimulation'.

5.4.4.2 *A flexor / extensor bias*

It has been suggested by Foysal and colleagues that there may be a bias in the motor system towards the facilitation of flexor muscles over extensor muscles [153]. They showed that paired stimulation of either the extensor (EDC) or flexor (FDS) muscle, led to facilitation of the flexor only. A similar effect has been shown by others. For example, Godfrey et al. demonstrated using a tracking task, in which either the EDC or FDS muscle was the prime mover, that regardless of which muscle was used, FDS showed greater increases in cortical excitability than EDC [154]. This led them to conclude that "*the action of the muscle as a flexor vs. extensor may be one modulator of the immediate physiological effects of repetitive movement*". A similar effect was shown by Yamaguchi et al. who showed that stimulation of the flexor

muscle led to a depression in the extensor muscles [136]. Here the authors ascribed the effect to reciprocal pathways. The inclusion of voluntary or descending commands may be important, as Tinazzi and colleagues demonstrated that transcutaneous electrical nerve stimulation (TENS) stimulation of the flexor carpi radialis (FCR) muscle at rest, led to a reduction in FCR MEP amplitude and an increase in extensor carpi radialis brevis muscle (ECR) MEP amplitude [155].

Further evidence of asymmetry in the mediation of extensor and flexor muscles comes from Lackmy-Vallee et al [156]. They showed opposite modulation of reciprocal inhibition in extensor and flexor muscles in the wrist following transcranial direct current stimulation (tDCS) to the motor cortex. That is, a reduction in reciprocal inhibition directed from flexors to extensors, and an increase in reciprocal inhibition directed from extensors to flexors.

This asymmetry can also be observed in group III and group IV afferents. Martin et al. [157] reported that during maintained ischaemia of elbow muscles following a fatiguing exercise, inputs from group III and group IV afferents depress extensor but facilitate flexor motor neurons, as measured using cervicomedullary motor evoked potentials (CMEPS). Although, as it is not anticipated that such high levels of fatigue are present in this study, the action of group III and IV afferents may be limited.

Finally, it has been reported that non-human primates with a corticospinal tract lesion show a bias during recovery towards the strengthening of flexor over extensor muscles [158]. The authors point to the role of the reticulospinal tract as the possible source of this imbalance, although they emphasise that it should not simply be seen as the product of greater connectivity to flexor muscles from the reticulospinal tract, as the rubrospinal tract has a bias towards extensor connectivity, but still shows a preference towards flexion during recovery after injury.

This asymmetry of the networks controlling extensor and flexor muscles has important consequences for plasticity protocols. It is clear that the spinal networks and cortical connections are not pre-wired and static [159], and contain a complex network of connections and pathways, whose interactions need to be better understood to allow the development of targeted stimulation protocols and better interpretation of recorded outcomes. Nevertheless, the correlation between the data found in this study and the other plasticity studies discussed, suggests that the intervention is activating similar plasticity mechanisms.

5.4.4.3 *Further observations*

Foysal and colleagues also reported two other results of note [153]. Firstly, repetitive TMS led to facilitation of all measured muscles. This could be considered comparable to voluntary cortical activity, and this broad facilitation of all muscles is mirrored in the ‘no stimulation’ condition presented here. Secondly, both plasticity protocols, stimulating either the extensor or flexor muscle, led to significant facilitation of FDI and APB muscles. This shows that changes in excitability may reach further than the stimulated muscles and their antagonists.

5.4.4.4 *How does this relate to people with neurological conditions?*

This study was completed with healthy able-bodied volunteers, and whether the motor system of a neurologically impaired participant would respond in a similar manner is unknown. However, it is not unreasonable to believe that parallels would exist, and here we briefly outline how the changes in corticospinal excitability and baseline EMG might translate to rehabilitative outcomes.

The ‘stimulation during rest’ condition showed a significant reduction in baseline flexor muscle EMG activity, which could indicate a reduction in resting tone. This can be compared with Botulinum toxin which is used to reduce muscle tone in people with spasticity, and in a recent case study of an individual with chronic stroke, Botulinum toxin injections into the flexor muscle were reported to improved grip release times and shortened EDC activity during an initiation/release reaction time task [125, 160]. This demonstrated that reductions in muscle tone in the antagonist muscle, may lead to improvements in the control of the agonist. Moreover, although the efficacy of using Botulinum toxin to improve active upper limb function is debated [161], if the ‘stimulation during rest’ condition does reduce baseline EMG and therefore muscle tone, this is a possible mechanism by which the ‘stimulation during rest’ intervention could bring about positive rehabilitative outcomes.

The underlying mechanism of spasticity is understood to be hyper-excitable stretch reflexes [162], and has been ascribed to changed descending inputs to spinal circuits [163]. In particular, it has been suggested that a loss of cortical facilitatory input to dorsal reticular spinal tract, which provides a dominant inhibitory effect on spinal stretch reflexes, results in this hyper-excitability of stretch reflexes [163]. The conditions ‘stimulation with movement’, ‘no stimulation’ and ‘delayed stimulation’ all led to significant facilitation of corticospinal excitability of the flexor muscle. It is possible that this may reflect facilitated cortical activity, which via projections to the dorsal reticular spinal tract, could lead to changes in spasticity.

Furthermore, as MEP amplitude and resting motor threshold have both been linked with spasticity and other motor performance measures following stroke [164], facilitated corticospinal tract activity could indicate other improvements. However, this is highly speculative, and would require further testing, for example, by combining neurophysiological and functional assessments in a study with chronic stroke survivors, with subsequent investigation of correlations between these different outcome measures.

An alternative explanation for the modest improvements seen in some participants with neurological conditions, is that the intervention was creating a differential response between the extensor and flexor muscles. Upper limb impairment can be exacerbated by co-contractions, for example, an attempt to extend the hand leads to concurrent activation of the hand flexors preventing this motion [125]. An intervention that facilitates one muscle, whilst either depressing or holding input to the other constant, may help to individuate those muscles and reduce co-contractions. This is similar to an approach being used by Wright et al. [165]. They mapped EMG signals to control cursor movements on a screen, and specifically mapped co-activating muscle pairs in different directions. In a small pilot study they showed that 3 out of 5 stroke survivors had an objective reduction in arm impairment.

5.4.4.5 The wider context

The findings presented here contrast with other researchers who have reported increases in MEPs in the stimulated muscle following FES interventions [74, 115, 135, 146]. However, the details of each stimulation protocol are crucial for accurate interpretation, and may be viewed differently in the context of an extensor / flexor bias. For example, McGie et al. stimulated extensors, flexors and thumb muscles, and reported MEPs from APB, which as discussed above, might be facilitated regardless of whether the extensor or flexor muscle is stimulated [74]. Barsi and colleagues also reported facilitation of flexor muscles following therapeutic FES [135]. However, they provided FES to both extensors and flexors during a grasping task. They also included an FES at rest condition, which similar to the ‘stimulation during rest’ condition reported here, did not show any significant changes in cortical excitability. However, in contrast, their voluntary movement only condition also showed no significant changes. This may highlight the importance of the task used during training, as Perez et al. have previously highlighted the importance of skilful versus non-skilful training when investigating changes in MEPs [166].

Thompson and Stein showed MEP facilitation following FES in the tibialis anterior muscle (ankle flexor) and its antagonist soleus muscle (ankle extensor) following walking with FES [146]. MEPs were recorded using a 15% MVC contraction which may be important, as post-exercise depression has been shown to be absent in a contracted muscle [144]. It may also indicate differences in the upper and lower limb. These differences between stimulation protocols and interventions make comparisons with the literature challenging and highlights the need for further studies, and a possible review, to elucidate the relationship between plasticity, extensor and flexor muscles, and stimulation timing.

5.5 Conclusion

Contrary to our hypothesis, movement concurrent with stimulation was found to significantly facilitate corticospinal excitability of the unstimulated antagonist flexor (FDS) muscle, and either suppress or not change corticospinal excitability of the stimulated extensor (EDC) muscle. Furthermore, refinement of the relative timing of the task cue and the onset of stimulation, led to significant additional facilitation of corticospinal excitability of the flexor muscle compared to the original protocol. On average, facilitation in this refined condition lasted for at least 30 minutes, but was also associated with an increase in baseline EMG activity.

This study adds to growing body of evidence of a bias in the motor system towards facilitating flexor muscles (over extensor muscles) following injury or interventions designed to drive associative plasticity. We suggest that this result could be relevant to upper limb rehabilitation, as the differential activation of the flexor and extensor muscles may lead to improved individuation of muscles, and / or the increased corticospinal excitability of flexor muscles may indicate changes in supraspinal and spinal networks that could alter the hyper-excitability of spinal circuits associated with spasticity.

Facilitation of the flexor muscle can also be induced by exercise alone, but for impaired individuals, FES concurrent with movement can replicate this effect, or if stimulation is timed to converge with voluntary commands in the spinal cord, potentially enhance it. Contrastingly, the ‘stimulation during rest’ condition did not lead to facilitated flexor activity, but a significant reduction in baseline activity for at least 30 minutes. This could indicate a reduction in resting muscle tone and be a mechanism by which spasticity may be reduced following passive FES.

Chapter 6

An exploration of transcutaneous spinal cord stimulation for applications in upper limb rehabilitation

Aim:

- To develop an understanding of the potential of transcutaneous spinal cord stimulation (tSCS) for upper limb rehabilitation.

Objectives:

- Conduct a study in healthy able-bodied participants to develop an understanding of the effect of different parameters such as frequency, amplitude and pulse width on the comfort of the technique
 - Examine motor responses for indications of which neural structures may be stimulated by tSCS.
-

Acknowledgements / contributions: Many thanks to Digitimer Ltd for the loan and modification of a DS8R stimulator for this project. The dataset presented in this chapter was previously reported in George Evan's MRes thesis. Alongside Andrew Jackson, I supervised George during his MRes project. George was responsible for recruitment and conducting experiments. He completed his own analysis, discussion and conclusions, which are available in his MRes thesis. I initiated the project, prepared all the experiments and analysis scripts, and completed the analysis and discussion presented in the following chapter. George, Andrew Jackson, Mark Baker (Consultant Clinical Neurophysiologist/Neurologist) and I contributed to the design of the study and the ethics process. I would also like to thank Lynsey Duffell and Yazid Al'joboori at UCL for inviting me to take part in their lower limb tSCS study. Further thanks to Mark Baker for his comments on this chapter and throughout the study.

6.1 Introduction

Non-invasive transcutaneous spinal cord stimulation (tSCS) is an exciting new avenue of research that may be a game-changing technology in neurological rehabilitation for spinal cord injury (SCI) [57, 59-62, 100, 167]. While its origins can be traced back to the 1980s and 90s [168, 169] more recently, Edgerton et al. [57] have reported that the pain threshold for transcutaneous pulse-modulated high frequency (10kHz) stimulation is higher than with standard low frequency stimulation protocols. This has consequently been termed ‘pain-free’ stimulation and reportedly enabled stimulation at the higher currents necessary for targeting the spinal cord. Moreover, they have suggested that tSCS may be effective in improving function in humans with paralysis after SCI [60, 62, 63], with a reported 225% increase in grip strength (without simultaneous stimulation) following 8 sessions of stimulation combined with 4 weeks of training (n=8) [61], and in one participant following a similar intervention, a 10 point increase in upper extremity motor score [60]. Further to this, spinal cord stimulation (SCS) has more broadly been associated with pain relief [170], epilepsy [171] and gait dysfunction in advanced Parkinson’s Disease (PD) [172], and could be suitable for use in closed-loop and wearable devices. In particular, epidural SCS is currently the topic of high impact research investigating the rehabilitation of locomotion following SCI [51, 173].

Novel stimulation techniques like tSCS could be adapted for interventions such as the one introduced in this thesis; possibly either as a substitute for functional electrical stimulation (FES), or to complement it. However, before this can take place, studies must be completed to characterise different tSCS parameters, such as pulse width, frequency and amplitude, to understand which are best suited to rehabilitative applications.

This chapter describes a preliminary investigation into three different tSCS protocols, focusing on the comfort of the intervention and whether motor responses recorded during stimulation can provide insights into the underlying mechanisms of the technique.

6.2 Methods

6.2.1 Participants and study setting

Healthy abled-bodied volunteers were recruited at the Institute of Neuroscience, Newcastle University. Participants were over 18 years old, and able to give informed consent. Recruitment was subject to the following exclusion criteria: pregnancy, and any current or history of: cardiac

disease, neurological disease or disorders, epilepsy, SCI, arm, shoulder or neck injury. The study received ethical approval by the local ethics committee at Newcastle University.

6.2.2 Assessment of comfort

Participants were asked to rate the comfort of each stimulation train (described below) on a scale of 0 to 100, where 100 equated to their limit of mild discomfort. Participants were advised that they could stop the intervention at any time, stimulation should not be greater than mild discomfort, and that any stimulation found to be greater than mild discomfort would not be repeated. The protocol was designed such that the most comfortable stimulation frequency (lowest) was delivered first, allowing the participant to progressively assess if their limit of mild discomfort was being reached.

6.2.3 Transcutaneous spinal cord stimulation

Transcutaneous spinal cord stimulation (tSCS) was delivered using a DS8R Biphasic Constant Current stimulator (Digitimer Ltd.) modified by the manufacturer to enable stimulation at frequencies up to 10kHz. The cathodal electrode (5x5cm Axelgaard PALS Electrode) was placed over the C7 spinous process under flexion (the neck was returned to the neutral position for the study), and 2 x anodal electrodes (9x5cm Axelgaard Valutrode) were placed over the Iliac Crests. This is similar to the placements reported in [61]. The participant was seated at a table, with arms at rest on a cushion placed in front of them.

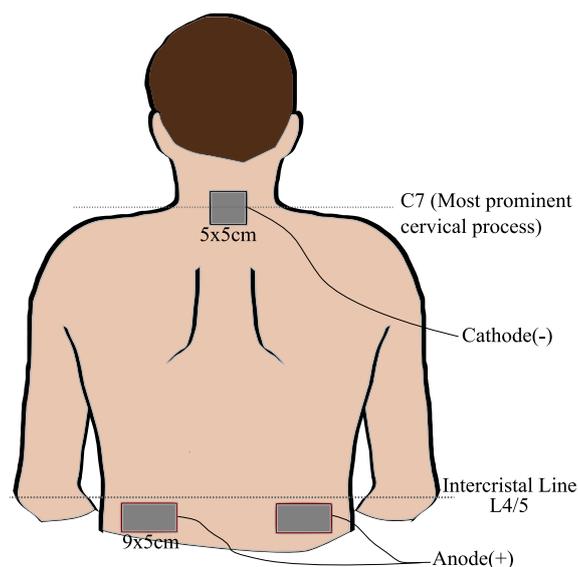


Figure 6-1: A schematic diagram to show approximate electrode positions used in this study

The cathode was placed over C7, which is the most prominent cervical process when the neck is flexed. The anodes were placed over the iliac crests, which sit below the intercrystal line, and avoided muscles which would otherwise be stimulated if located under the anodal electrodes.

6.2.4 Experimental protocol

Three different stimulation types were used:

1. ‘Conventional’ stimulation – Single monophasic pulse (pulse width 0.5ms)
2. ‘Burst’ stimulation – Pulse-modulated high frequency monophasic stimulation (10x stimuli with pulse width 50 μ s)
3. ‘Single’ stimulation – Single short monophasic pulse stimulation (1x stimulus with pulse width 50 μ s).

Examples of these are shown in Figure 6-2.

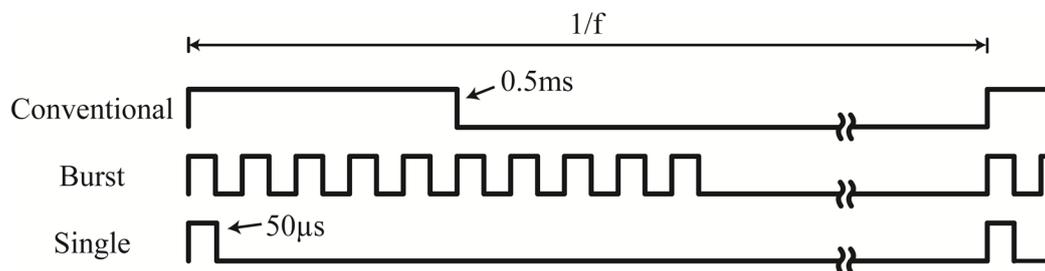


Figure 6-2: The three different types of stimulation used during this study

‘Conventional’ stimulation consisted of a 0.5ms monophasic pulse, ‘burst’ stimulation consisted of a series of ten 50 μ s pulses, and ‘single’ stimulation was a single 50 μ s pulse.

Resting motor threshold was found for each stimulation type for each participant, where threshold was defined as the current needed to evoke a MEP in 50% of trials in a single muscle (of the eight recorded) [174]. To investigate the impact of different stimulation parameters on comfort and motor responses, the protocol was divided into three sub-sections depending on the frequency, amplitude relative to resting motor threshold, and the duration of the stimulation delivered. The three study sub-sections were as follows (also see Figure 6-3):

1. Participants received each stimulation type in a block. The order of these blocks was randomised for each participant, for example: 1. ‘burst’ stimulation; 2. ‘conventional’ stimulation; and 3. ‘single’ stimulation. Trains were delivered for 0.5s for frequencies from 10 to 100Hz, and repeated three times. Stimulation was also delivered at 0.5Hz as a train of 5 stimuli. The stimulation amplitude was 110% of resting motor threshold for that stimulation type (i.e. 1.1 times the stimulation magnitude at resting motor threshold).

- The participant received each stimulation type at 100Hz for 2s at 110% of resting motor threshold.
- The participant received ‘conventional’ stimulation at 90, 100, 110, 120, 130 and 140% of resting motor threshold for 0.5s at 100Hz

At the end of each 0.5s or 2s stimulation train the participant was asked to rate the comfort of the stimulation (as previously described). There was a minimum of 5 seconds between trains. The null hypothesis was that there would be no significant difference between the comfort scores when: (1) changing the stimulation frequency, (2) changing the stimulation intensity, (3) changing the stimulation duration, or (4) changing the stimulation profile (i.e. conventional vs. burst vs. single).

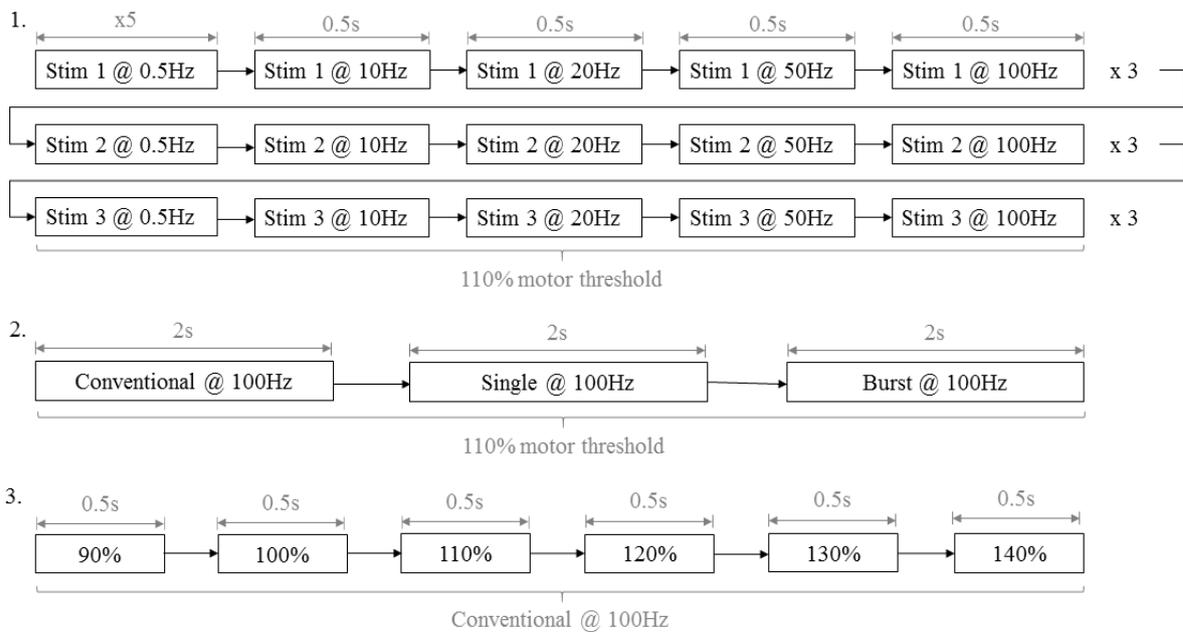


Figure 6-3: The stimulation protocol used in this tSCS study

1. The different stimulation types were randomised as either Stim 1, Stim 2 or Stim 3 at increasing frequencies and delivered for 0.5s or as a train of 5 stimuli (0.5Hz only) three times at 110% of motor threshold. 2. Each stimulation type was delivered once for 2s at 100Hz and 110% of motor threshold. 3. Conventional stimulation was delivered at 100Hz for 0.5s at increasing intensities relative to motor threshold.

6.2.5 Recording motor responses to transcutaneous spinal cord stimulation

Responses to tSCS were recorded using bipolar electromyography (EMG). EMG was collected using a Digitimer D360 amplifier, a CED MICRO2 1401 with ADC12 Expansion data acquisition interface (Cambridge Electronic Design Ltd.) and Spike2 software (Cambridge

Electronic Design Ltd). The sampling rate was 5000Hz, and the signal was filtered with a low frequency cut-off of 30Hz and a high frequency cut-off at 2000Hz. Responses were recorded from eight muscles using surface electrodes (Natus Disposable Snap Electrodes 33x22cm). The muscles were: flexor digitorum superficialis (FDS), extensor digitorum communis (EDC), first dorsal interosseous (FDI) and abductor pollicis brevis (APB) on both the left and right hand sides. Stimulus artefacts were blanked by removing the data points before and after the stimulus, and then interpolating across the resulting gap.

This dataset was imported into MATLAB (The MathWorks Inc.) for offline analysis of responses. The size of individual responses to 0.5Hz stimuli was assessed by averaging the peak-to-peak motor evoked potential (MEP) elicited by each stimulation type. To compare across participants, this was presented as a percentage of the average response to ‘conventional’ stimulation. Unless otherwise stated, statistical tests were conducted in IBM SPSS 24.

6.2.6 Data analysis of oscillatory motor responses

An unexpected oscillatory response was observed during the study. To quantify how often this response occurred, and to test for significance across a range of frequencies, a bootstrap statistical approach was used.

The EMG signal for first 0.5s stimulation train for each stimulation type (‘burst’, ‘conventional’, ‘stim’) and test frequencies above 10Hz (20, 50 and 100Hz) was divided into windows equal to the inter-stimulus interval. The windows were randomly shuffled, zero-meaned and rectified, and the power spectrum for the resulting signal was found using a Fast Fourier Transform (FFT) in MATLAB. This was repeated 1000 times, and for each power spectrum frequency the power was ranked in ascending order. The power spectrum of the original EMG signal was then found, and if the power at a particular power spectrum frequency in the original trial was greater than the value of the 975th power value in the shuffled trials, then it was considered to a significant trial with a ‘P’ value less than 0.05. This is illustrated in Figure 6-4. The null hypothesis was that no power spectrum frequency would show a statistically significant number trials containing oscillations at that frequency.

Each muscle was treated as a separate trial, and as there were 8 participants and 8 muscles, there were 64 trials for each test frequency (20, 50 and 100Hz). Therefore, the percentage of trials showing significant oscillatory behaviour at each power spectrum frequency was found, allowing the number and frequency of oscillatory responses to be quantified.

This method was also repeated for the increasing intensity dataset (see Figure 6-3, 90 to 140%), allowing additional analysis on the effect of intensity, participant and muscle on the quantity and frequency of oscillations to be assessed. This produced a total of 64 trials for each intensity (8 participants, 8 muscles), 48 trials for each participant (6 intensities, 8 muscles) and 48 trials for each muscle (8 participants, 6 intensities).

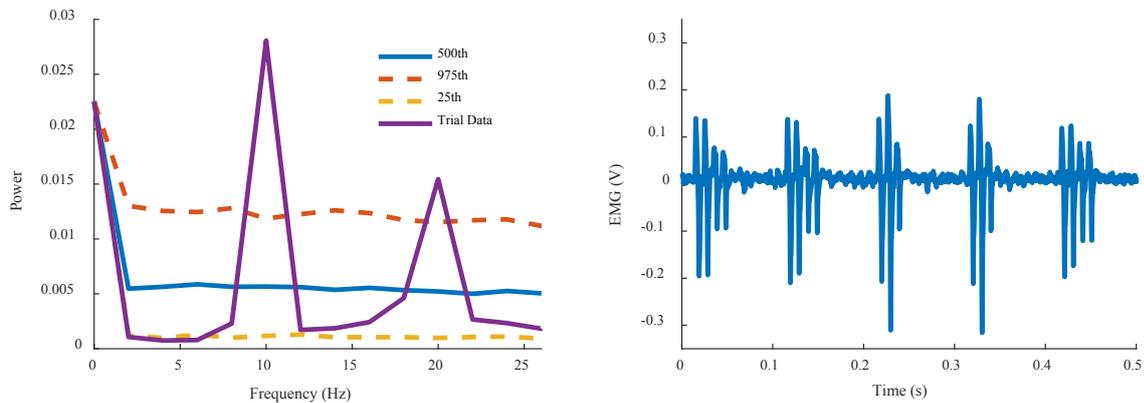


Figure 6-4: An example of the bootstrap statistical method used for data analysis

Panel A – The power spectrum of a 0.5s trial showing a statistically significant peak at 10Hz and a harmonic at 20Hz. The red, blue and yellow dashed lines show the power of 975th, 500th and 25th ranked powers for each power spectrum frequency respectively. These were found using the bootstrap methodology described above. If the power spectrum of the original 0.5s trial falls outside the red and yellow dashed lines at any frequency, then it is significant at this specific frequency with $P < 0.05$. It can be seen that this trial contained significant oscillatory behaviour at 10 and 20Hz. Panel B - The corresponding example EMG signal showing a clear oscillatory response.

The synchrony between oscillations in two muscles during a single 0.5s stimulation train were compared (in one instance) to investigate the possibility of a common driver. The two 0.5s trains were zero-meaned and rectified before being low-pass filtered at 15Hz (Butterworth, 2nd order, zero-phase digital filter), and zero-meaned again. The phase angle was then found using a Hilbert Transform. The output of this analysis is shown in the results section (Figure 6-15).

6.2.7 Additional measures

A small number of control studies were carried out using peripheral nerve stimulation (PNS), tSCS with Poisson firing (see description below) and a small sustained contraction (without stimulation) to allow comparison between tSCS motor responses and those induced by these methods.

- PNS was delivered using the Digitimer DS8R (0.5ms pulse width) at 100Hz in a 2s train to median nerve using a bar electrode to stimulate the APB muscle at an intensity that evoked a response of approximately the same magnitude as that observed during

tSCS. The power spectrum of the resulting EMG signal was found using a Fast Fourier Transform (FFT) in MATLAB, and significance was tested as described above (bootstrap method).

- tSCS with Poisson firing: Trains in the main study were delivered with evenly spaced stimuli at a particular test frequency. Here, stimulation timing was controlled using a Poisson process, i.e. the probability of stimulation per time interval was constant, but the average stimulation rate was approximately 100Hz. For this condition, a minimum time interval between stimuli was set at 5ms and a ‘conventional’ stimulation pulse width (0.5ms) was used. Stimulation timing was controlled in Spike2 (Cambridge Electronic Design Ltd.). The power spectrum and significance were calculated as described above.
- A gentle, sustained contraction: the participant performed a 2s gentle sustained thumb extension which was recorded (EMG) from the APB muscle. The power spectrum and significance were calculated as described above.

6.3 Results

Eight participants (7 male, 26.5 ± 1 years (mean \pm SE), all right-handed) gave written informed consent and took part in the study. Seven of the participants were members of the motor group at Newcastle University’s Institute of Neuroscience.

6.3.1 Parameters

Figure 6-5 shows the average current required to achieve resting motor threshold in at least one muscle for each stimulation type. A statistically significant difference was found for comparisons between each stimulation type: burst-single, conventional-burst, and single-conventional, demonstrating that the threshold current is specific to each stimulation type, and that bursts of stimuli have a lower threshold than a single stimuli of the same pulse width (‘burst’ vs. ‘single’), showing an accumulating effect of successive stimuli.

The size of motor responses (peak-to-peak) evoked at 110% of threshold for the three different stimulation types relative to ‘conventional’ stimulation are shown in Figure 6-6. These were calculated using stimulation delivered at 0.5Hz and with the muscle found to have the greatest response at threshold for the ‘single’ stimulation type. As anticipated, at 110% of threshold for each stimulation type, there are no statistically significant differences between motor responses.

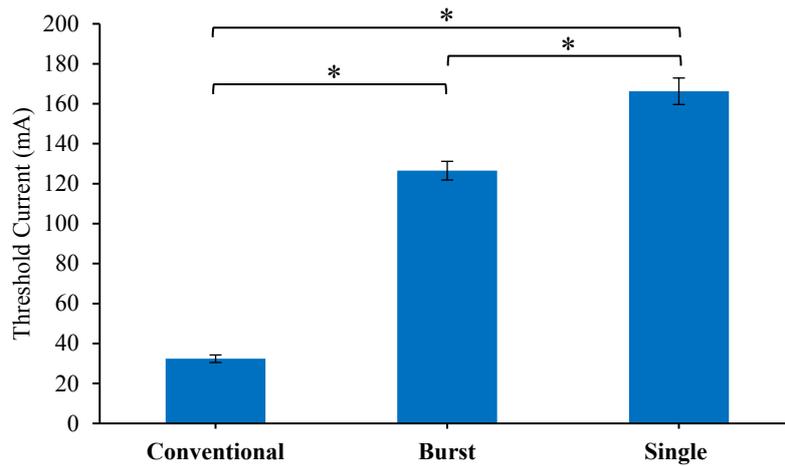


Figure 6-5: The average current required at resting motor threshold for each stimulation type
 Error bars show standard error. A Wilcoxon signed-rank test was conducted to test for significance between groups. Following a Bonferroni correction for multiple comparisons, significance was defined as $P < 0.017$. A statistically significant difference was found for all comparisons: burst-single ($P = 0.012$), conventional-burst ($P = 0.012$), and single-conventional ($P = 0.012$).

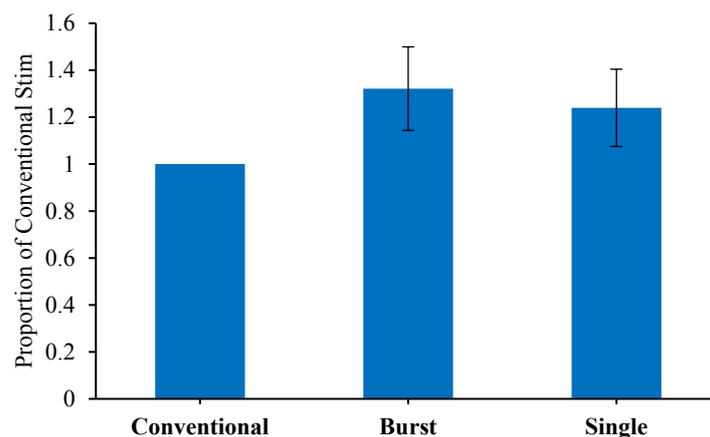


Figure 6-6: The average motor evoked response, of the muscle identified at threshold for the 'single' stimulation type, as a proportion of its response to 'conventional' stimulation
 The average motor evoked response (peak-to-peak) to 0.5Hz stimulation at 110% of threshold in the muscle with the greatest response at threshold for the 'single' stimulation type (8 participants, 1 muscle each, average of 15 responses). Results were normalised to the 'conventional' stimulation type response to allow comparison across participants. Note that typically the same muscle was found to give the greatest response at threshold across all stimulation types ('conventional', 'burst', 'single'), but where variations were recorded, the 'single' stimulation type was used for this analysis. A Wilcoxon signed-rank found no statistically significant difference between the groups (Bonferroni correction for multiple comparison, $P < 0.017$): Single-to-Conv ($P = 0.3125$), Burst-to-Conv ($P = 0.0781$) and Single-to-Burst ($P = 0.4609$). Statistical tests were conducted in MATLAB (The MathWorks Inc.).

6.3.2 Assessment of comfort

All participants completed the study and no major adverse effects were reported. Stimulation led to contraction of back and neck muscles, and this increased with amplitude, frequency and

duration. Despite being above motor threshold, no overt movements of the hand or arm were observed. Some participants noted a sensation at the back of the throat during higher frequency and amplitude stimulation. One participant reported mild tingling of the hands following stimulation, but this was believed to be caused by pre-existing external factors. Two scores of 100 were recorded in two participants indicating the limit of mild discomfort had been reached. The first during the intensity study at 140% of threshold, and the other, during a 2s train of burst stimulation. Any discomfort ceased as soon as the stimulation was removed.

The change in comfort score with stimulation frequency at 110% of resting motor threshold for each stimulation type is shown in Figure 6-7. It is evident that increasing frequency reduces comfort, and 'burst' stimulation was found to be statistically more comfortable than 'conventional' and 'single' stimulation. Figure 6-8 shows that there was no statistically significant difference in comfort if the duration was increased from 0.5 to 2s, and Figure 6-9 demonstrates that comfort was reduced by increasing stimulation intensity.

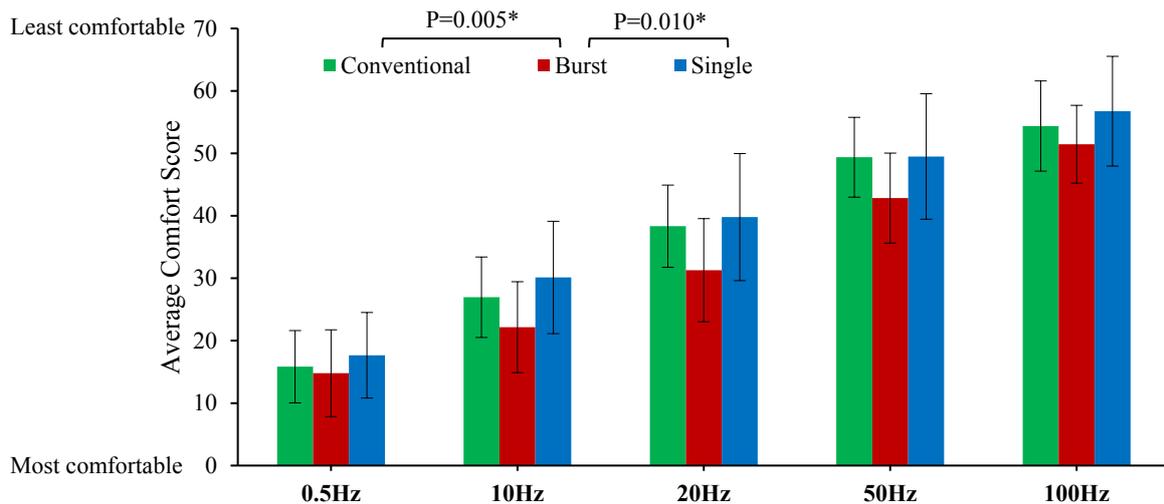


Figure 6-7: The average comfort scores for all participants

The mean score from the three repetitions for each stimulation type was found, and then averaged across participants. Error bars show standard error. A comfort score of 0 is the most comfortable, and a maximum score of 100 would indicate the limit of mild discomfort. A Friedman test was conducted for each stimulation type, and a statistically significant effect for frequency was found for each stimulation type (single $\chi(4)^2 = 29.7$, $P=6 \times 10^{-6}$; burst $\chi(4)^2=29.9$, $P=5 \times 10^{-6}$; conventional $\chi(4)^2=25.9$, $P=3.2 \times 10^{-5}$). A comparison between stimulation types across all frequencies (Friedman test), found a statistically significant difference for stimulation type ($\chi(2)^2 = 10.293$, $P = 0.006$). Pairwise post-hoc analysis (Dunn test) found statistically significant differences between conventional and burst ($P=0.005$), and burst and single ($P=0.010$) following a Bonferroni correction ($P_{sig}=0.017$). The difference between conventional and single was not significant ($P=0.823$).

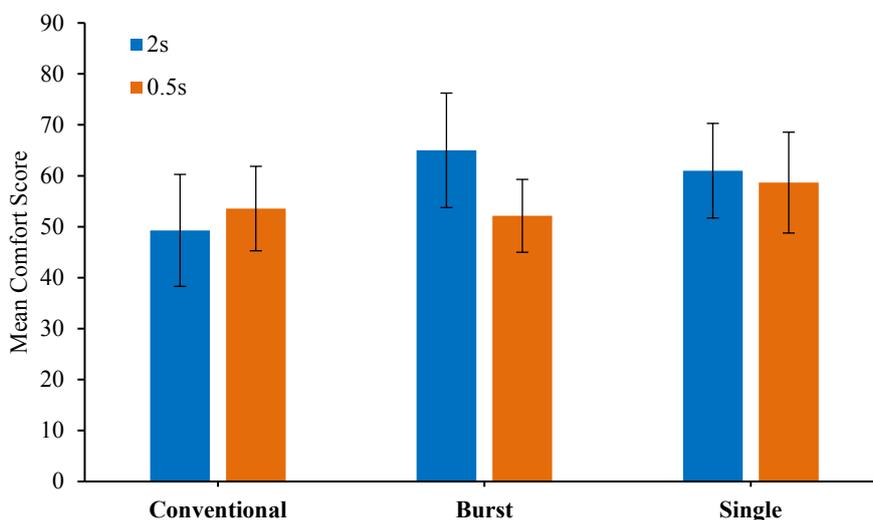


Figure 6-8: The effect of stimulation duration on comfort score

The average comfort score of stimulation at 110% of threshold for a 2s duration compared to a 0.5s duration. A comfort score of 0 is the most comfortable, and a maximum score of 100 would indicate the limit of mild discomfort. Scores were only available for 7 participants. Error bars show standard error. A Wilcoxon Signed-Rank test showed no significant differences between 0.5s and 2s in any stimulation type (left-to-right $P=0.672$, $P=0.176$ and $P=0.866$).

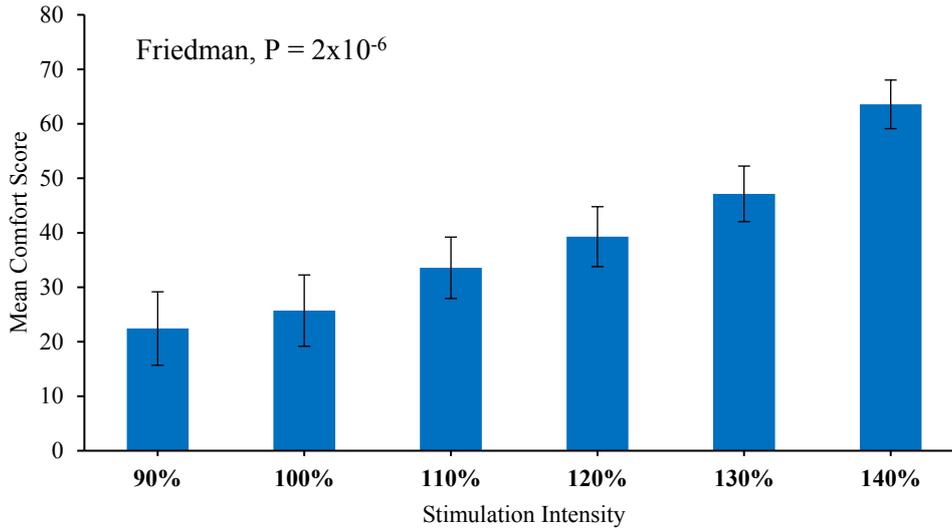


Figure 6-9: The average comfort score for increasing intensity

The intensity was increased from 90% of threshold to 140% of threshold for a 0.5s 100Hz train of ‘conventional’ stimulation. Scores were only available for 7 participants. Error bars show standard error. A comfort score of 0 is the most comfortable, and a maximum score of 100 would indicate the limit of mild discomfort. There was a statistically significant difference across all intensities (Friedman Test, $\chi^2(5) = 34.417$, $P=2 \times 10^{-6}$).

6.3.3 An unexpected oscillatory response

An unexpected oscillatory response was observed during the study. Examples are shown in Figure 6-10, Figure 6-11, and Figure 6-12. The frequency of oscillations and the percent of trials they appeared in was quantified using bootstrap statistical testing (see Figure 6-13 and Figure 6-14).

Oscillations were intermittently present in all stimulation types, with stimulation at 100Hz generating the greatest number of occurrences across all muscles (Figure 6-13). The number of significant occurrences was greatest for the ‘burst’ stimulation, with a tendency towards more 8Hz oscillatory behaviour in ‘single’ and ‘conventional’ stimulation types (Figure 6-13), although further testing would be required to draw stronger conclusions about this. As on average the ‘burst’ stimulation generated a larger MEP (see Figure 6-6), this might partially explain the greater number of oscillatory responses found for this stimulation type.

To demonstrate that this oscillation was driven by the stimulation and was not the product of an underlying tremor or ‘background noise’, the dataset from the increasing intensity study was analysed (Figure 6-14-A). The frequency of oscillations appears to be independent of intensity, which suggests a possible intrinsic oscillator. However, there is a peak and then drop-off in the number of significant trials between 120 and 140% (see Figure 6-14-A inset).

Instances of oscillations were found to intermittently occur in all muscles tested (Figure 6-14 – B) and typically, with a peak at 10Hz, although L-FDI (left hand FDI) and R-FDS (right hand FDS) peaked at 8 and 14Hz respectively. It might have been expected that the frequency of stimulation would vary with, say, proximal vs. distal muscles, as the reflex arc length changes, but this does not appear to be the case in this dataset. Instead, these instances of greater power at 8 and 14Hz may be the result of inter-participant differences (see Figure 6-14-C). Oscillatory behaviour was elicited in all participants, although some participants did show a larger number of significant trials (Figure 6-14-C).

Typically, oscillations appear to be driven by stimulation onset, i.e. the start of the oscillation corresponds to the first stimulus (Figure 6-10, Figure 6-11, and Figure 6-12). This suggests that this effect is not the magnification of on-going background oscillation. Despite being initiated in synchrony, in some cases, oscillations were observed to shift relative to one-another, this is shown in Figure 6-10 and Figure 6-15. Here, two muscles (L-FDI, L-EDC - Figure 6-15) appear to be oscillating at different frequencies, suggesting that they are acting independently and that there is not a common oscillator maintaining synchrony between these muscles, as might be expected with a central pattern generator (CPG). Furthermore, there are potentially two independent oscillators within the same muscle (R-APB, Figure 6-10). It is plausible that the different frequencies observed in different muscles are the result of different reflex loop path lengths, but as different frequencies may be present within the same muscle, the cause is less clear.

Synchronous oscillations were observed consecutively in agonist / antagonist muscle pairings, i.e. EDC and FDS - Figure 6-12), suggesting that this is not purely the activation of a stretch reflex loop or CPG which would be expected to inhibit the antagonist muscle.

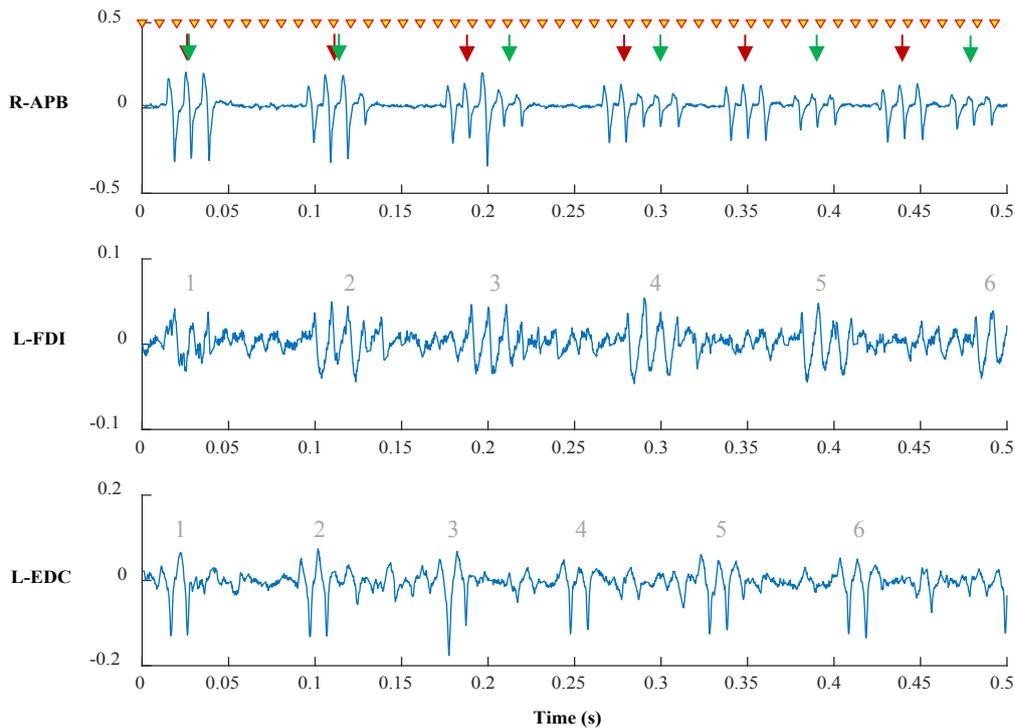


Figure 6-10: An example of oscillatory behaviour

Recorded during 0.5s of ‘conventional’ stimulation at 130% of motor threshold at 100Hz. R- indicates a muscle on the right hand side, and L- the left. In this example, there are approximately 6 oscillations in 0.5s period (12Hz). Stimulation timing is shown in red triangles and the y-axis shows the EMG signal in volts. The latency from the first stimulus to the first response is approximately 13.5ms, 12.5ms and 10.5ms for R-APB, L-FDI and L-EDC respectively (calculated by using the Spike2 graphical user interface (Cambridge Electronic Design Ltd.)). Two oscillations within the same muscle are highlighted in the R-APB (red & green arrows). The stimulus artefact has been blanked.

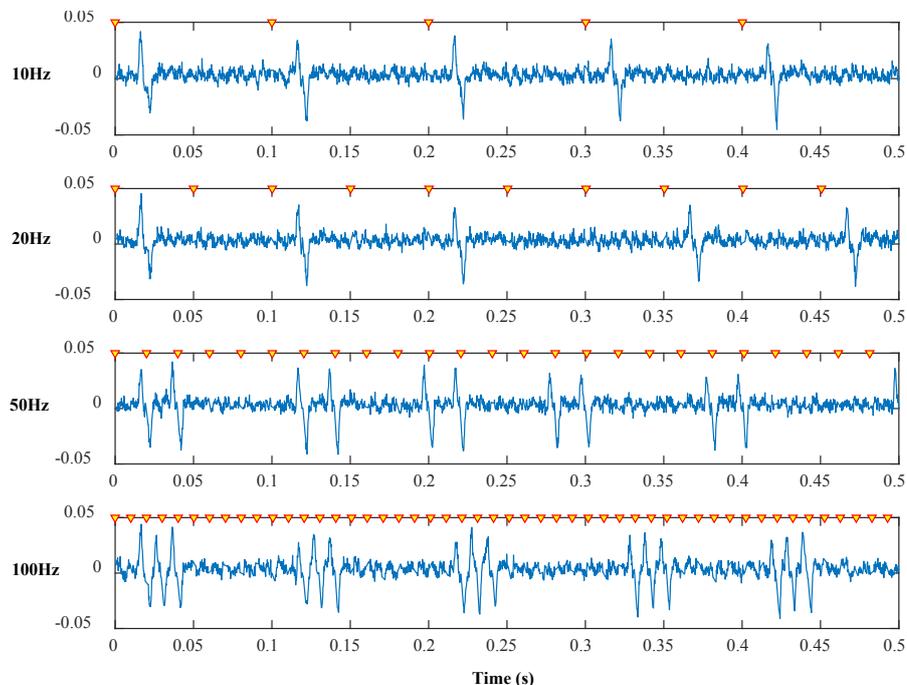


Figure 6-11: An example oscillatory behaviour at a range of frequencies

Recorded using ‘conventional’ stimulation, 110% of threshold, left-hand FDI. Each red triangle indicates a stimulus, and the y-axis shows the EMG signal in volts. The stimulus artefact has been blanked.

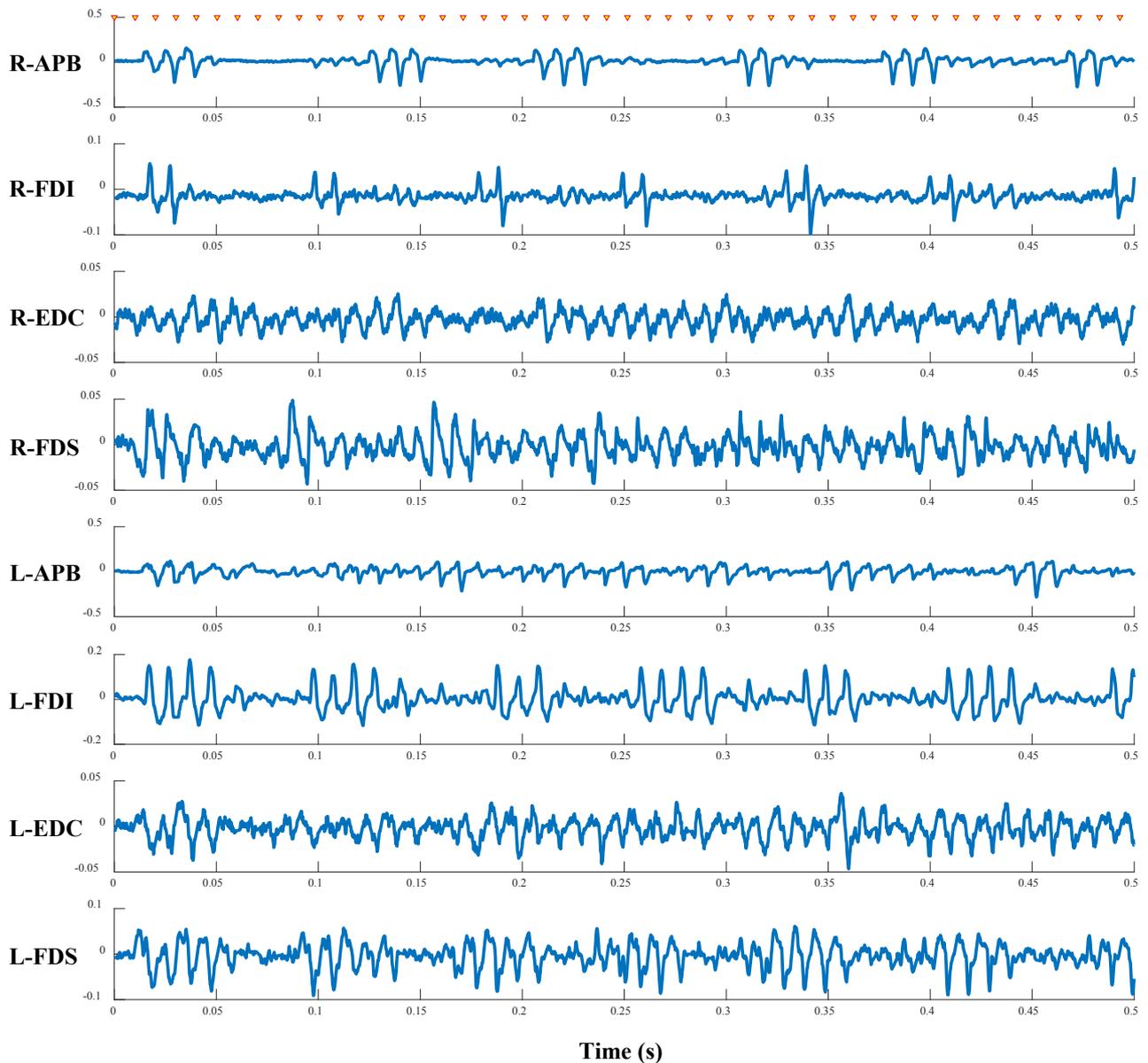


Figure 6-12: An example of strong oscillations across multiple muscles

A 0.5s EMG signal recorded using 'conventional' stimulation at 130% of threshold. Each red triangle indicates a stimulus, and the y-axis shows the EMG signal in volts. The stimulus artefact has been blanked.

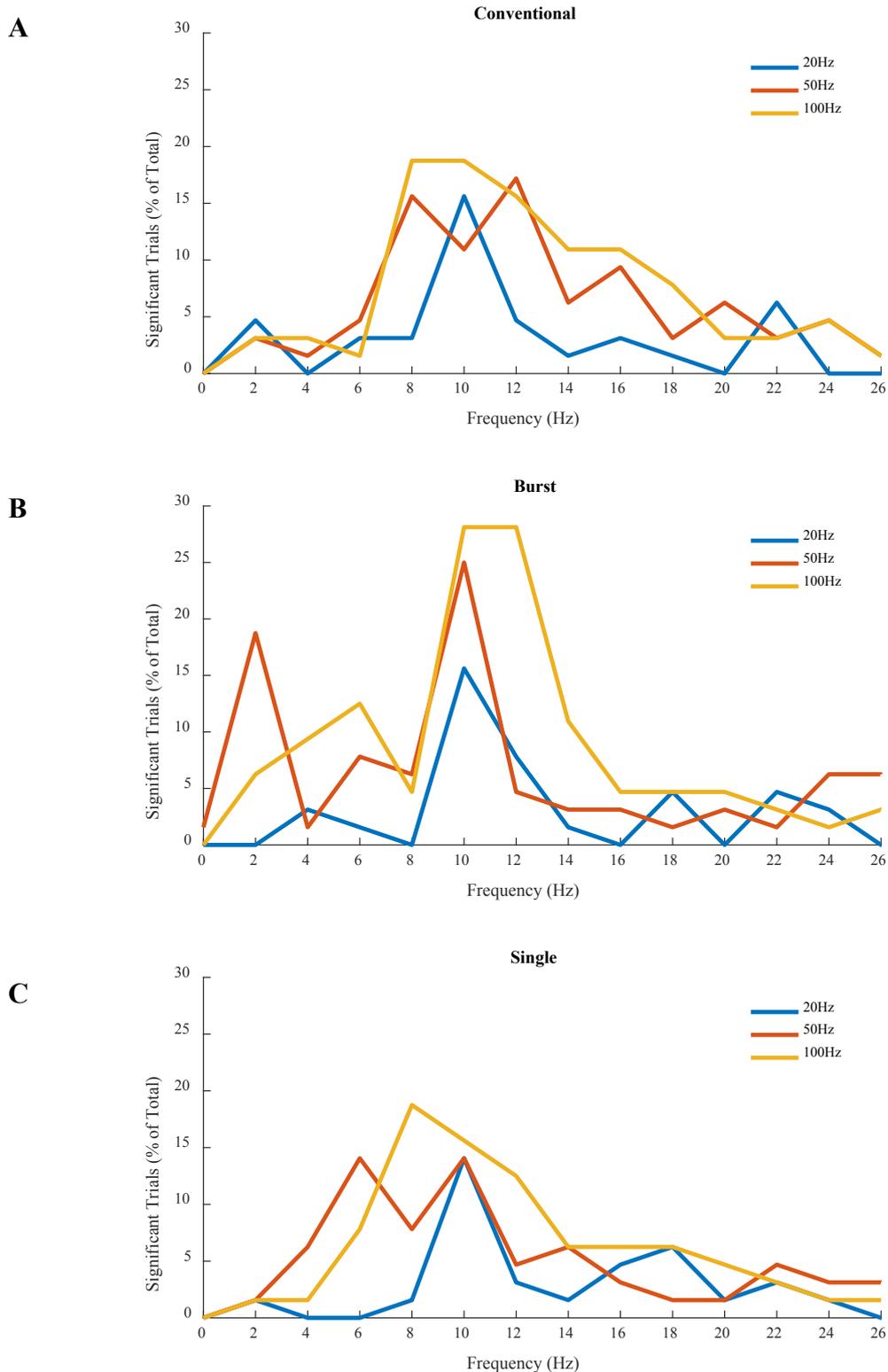


Figure 6-13: The output of bootstrap statistical testing of EMG collected during the first 0.5s stimulation train at each test frequency (20, 50, 100Hz) for each stimulation type ('conventional', 'burst', 'single') This analysis was conducted to identify which muscles showed significant oscillatory power over a range of frequencies. Each muscle was treated as a separate trial, giving 64 trials per test frequency and stimulation type (8 participants, 8 muscles). A peak in number of significant trials at particular frequency is associated with an unexpected oscillatory behaviour observed in the EMG signal during stimulation. The definition of a significant trial is given in 6.2.6.

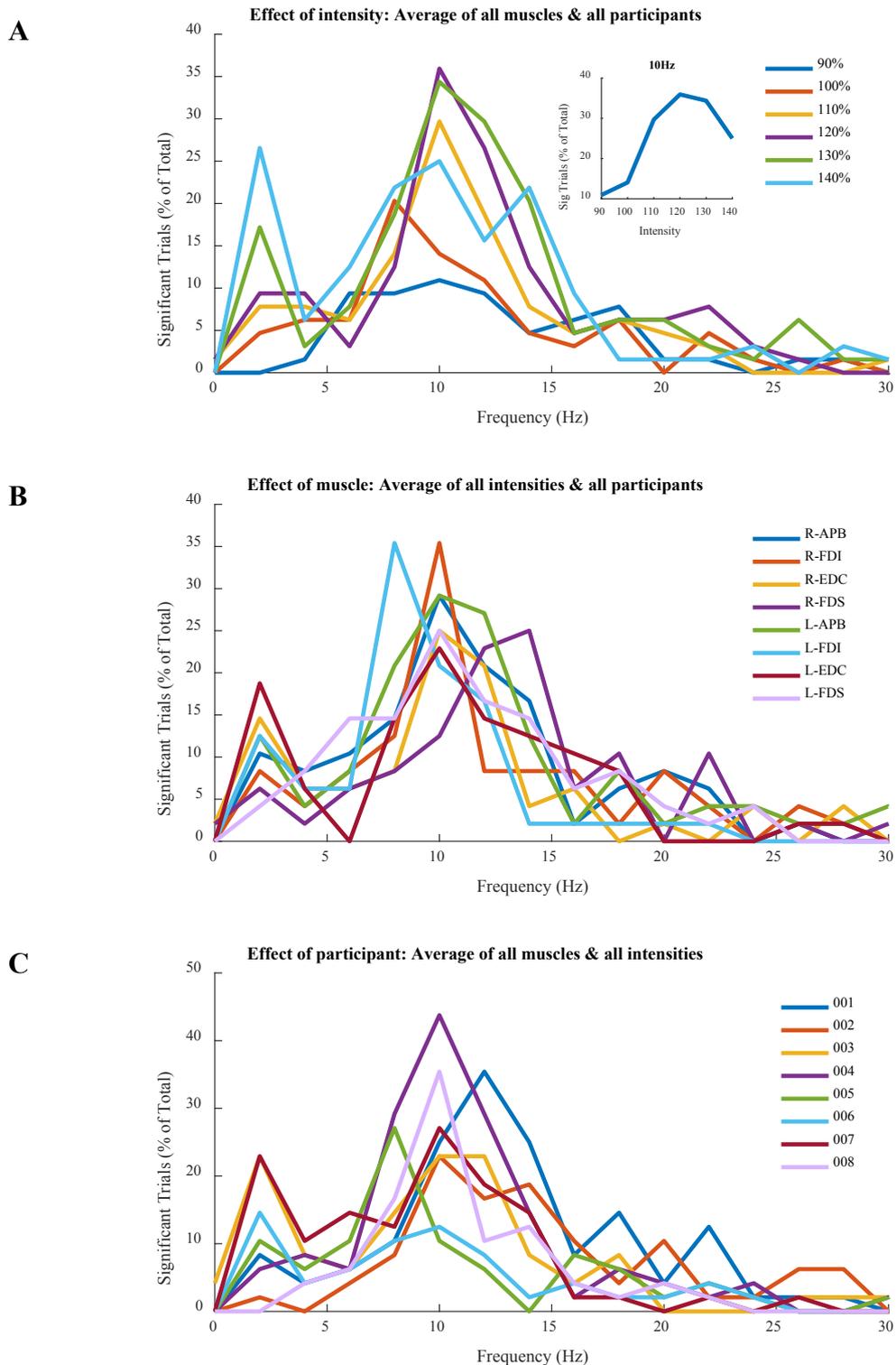


Figure 6-14: The output of bootstrap statistical testing of the EMG signals collected for 0.5s trains of 'conventional' stimulation at intensities 90 to 140% of resting motor threshold

This analysis was used to identify which intensities (A – 64 trials), muscles (B – 48 trials) and participants (C - 48 trials) showed significant oscillatory power over a range of frequencies. A peak in number of significant trials at particular frequency is associated with an unexpected oscillatory behaviour observed in the EMG signal during stimulation. The definition of a significant trial is given in 6.2.6. A-inset shows the number of significant trials at 10Hz as function of intensity. It peaks at 120% of threshold before dropping off at higher intensities. The peak at ~2Hz may be a consequence of the 0.5s trial length.

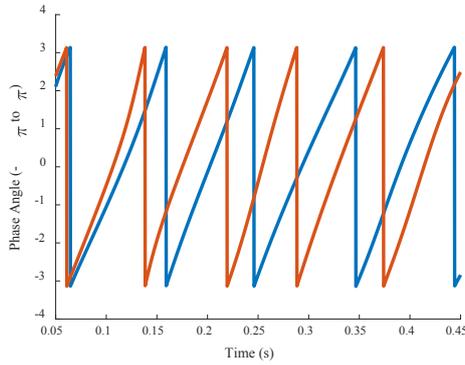
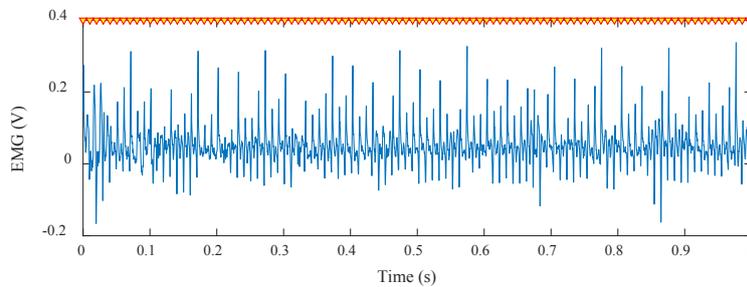


Figure 6-15: A plot showing the a-synchronous behaviour of two oscillations

Oscillations were recorded in the L-FDI (blue) and L-EDC (red) as shown in Figure 6-10. The phase angle (π to $-\pi$) for the two signals is shown at each time point. The first and last 50ms have been removed to avoid edge effects. It is evident that the frequency of the oscillation in the EDC is greater than that in the FDI, as the two signals drift in and out of synchrony.

Motor responses were collected from two participants using two different approaches to muscle activation: peripheral nerve stimulation (PNS) (Figure 6-16), and a gentle voluntary contraction (Figure 6-17), to compare the oscillations observed during tSCS with any oscillatory behaviour that might be induced by these methods. Additionally, tSCS was delivered using Poisson firing (Figure 6-18) to investigate whether continuous stimulation at a constant rate was the cause of oscillations.

A



B

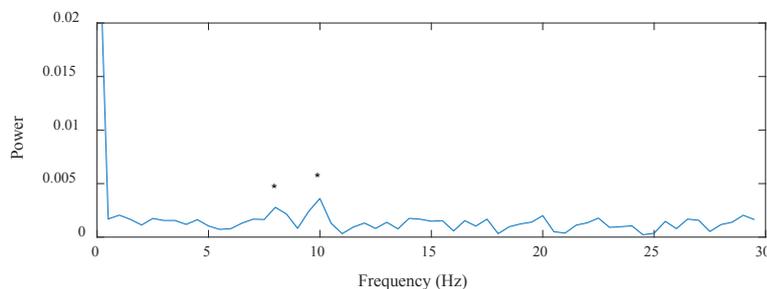


Figure 6-16: The oscillatory motor response to peripheral nerve stimulation at 100Hz

Panel A - The EMG signal from the right-hand APB for the first 1s of 2s of PNS delivered to the median nerve (participant #2). Red triangles indicate stimulation timing. Panel B - the corresponding power spectrum calculated using rectified EMG data for the 2s period. Statistical significance was tested using the previously described bootstrap approach with the signal divided into 10ms windows. P values < 0.05 are marked with an * (8Hz and 10Hz).

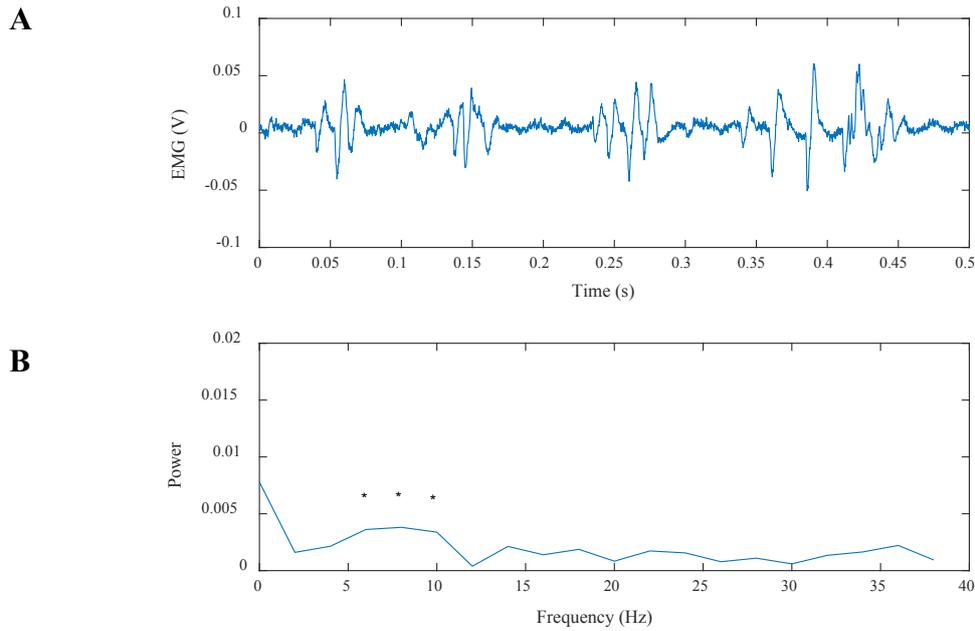


Figure 6-17: The oscillatory motor response to a gentle contraction

Panel A - The EMG signal recorded from right-hand APB during a gentle sustained extension of the thumb (participant #2). Panel B – The power spectrum of EMG signal with a small peak between 6 and 10Hz. This was found to be statistically significant ($P < 0.05$, marked with *) as tested using the previously described bootstrap approach with the signal divided into 10ms windows. Note that this example was selected from several contractions as it showed the most obvious oscillatory behaviour.

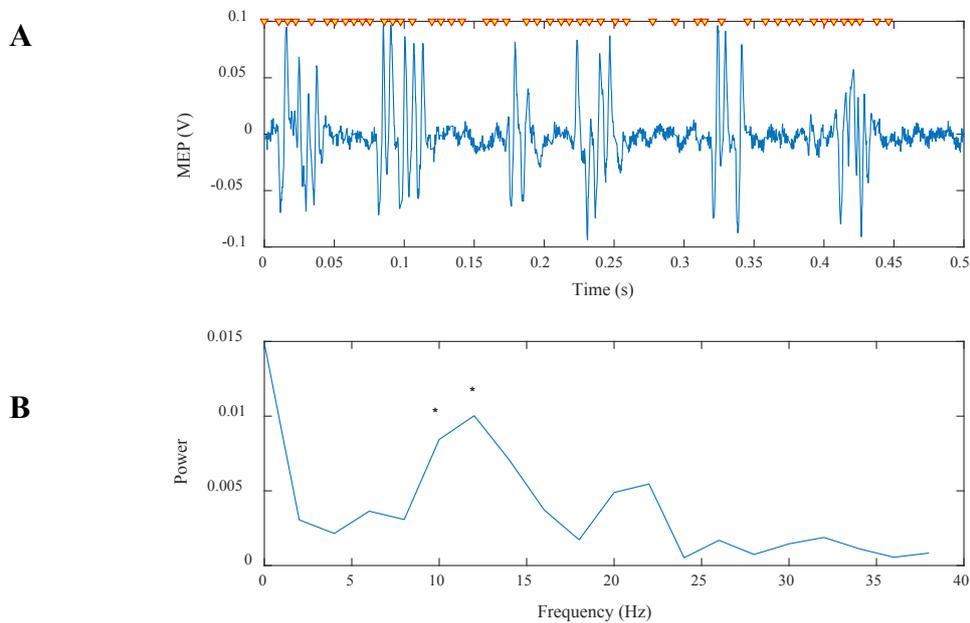


Figure 6-18: The oscillatory motor response to tSCS controlled by a Poisson process

Panel A – A 100Hz stimulation train with stimulation timing controlled by a Poisson process. Red triangles show the stimulation timing. Panel B - the corresponding power spectrum. This dataset was collected from participant #3, right-hand FDS, as this muscle had previously been shown to give a strong oscillatory response for this participant. Statistical significance was tested using the previously described bootstrap approach with the signal divided into 10ms windows. P values < 0.05 are marked with an * (10Hz and 12Hz).

6.4 Discussion

6.4.1 Comfort study

Pulse modulated high frequency stimulation ('burst') was significantly more comfortable than 'conventional' and 'single' stimulation across a range of frequencies from 0.5Hz to 100Hz at 110% of resting motor threshold for that stimulation type. There was no significant difference between 'single' and 'conventional' stimulation, suggesting that when different motor thresholds are accounted for, high frequency bursts of stimuli are more comfortable than trains of single stimuli. However, the mean difference between 'burst' and 'single' stimulation was just 6 points on the comfort scale, and between 'burst' and 'conventional' it was 4, which is only a small percentage of the total scale. As anticipated, increasing the intensity and frequency reduced the comfort of stimulation, but contrary to expectations, a longer stimulation duration did not lead to a reported increase in discomfort. Although, it should be noted that the 2s trains were delivered at the end of the session, and participants may have become more accustomed to stimulation by this point, and may not account for the time delivered in their assessment.

As anticipated, there was no significant difference in size of motor response elicited at 110% of resting motor threshold for the different stimulation conditions ('burst', 'conventional' and 'single' - Figure 6-6). However, there was a trend for 'burst' stimulation to deliver slightly larger responses, which might have been expected to lead to it being reported to be slightly less comfortable, but as discussed, the contrary result was found. It is suggested that the motor threshold reflects the stimulation magnitude required to elicit a posterior root reflex [101].

It was shown that high frequency bursts of stimuli elicit motor responses at a lower currents than a single stimulus of the same pulse width ('burst' versus 'single' - Figure 6-5). This demonstrated that the temporal summation of sub-threshold stimuli can lead to lower thresholds in terms of current amplitude. That is, a single 50 μ s pulse required a significantly higher current than a train of 50 μ s pulses at 10kHz to produce a similar motor response. This has previously been described as the Gildemeister effect [175]. Furthermore, the 'burst' stimulation type could be refined, as it is unlikely that 10 was the optimum number of stimuli, and any reduction in train length would be anticipated to increase comfort.

Therefore, there is evidence that 'burst' stimulation is more comfortable than a single stimulus, but the small benefits shown in this study do not necessarily justify the development of specialist technology to deliver pulse modulated high frequency stimulation. Nevertheless,

there are caveats to this statement. Firstly, stimulation was not applied with any refinement, such as the aforementioned reduction in train length or features such as ramping the stimulation on or off. It may be that ramping can improve comfort by reducing transient currents and that these improvements will create greater differences between stimulation conditions. Secondly, monophasic stimulation was used during this study, and it is possible that biphasic stimulation would show greater differences between stimulation types. However, anecdotal evidence from pilot work conducted in the laboratory suggested that biphasic stimulation was slightly less comfortable due to stimulation of back muscles proximal to the iliac crests.

The discomfort caused by the stimulation in this study was typically reported to be two-fold. The shock or surprise caused by an unexpected contraction of back and neck muscles, and the involuntary contraction of those muscles. The contractions may have been magnified by the use of a 5x5cm cathodal electrode over the C7 vertebra. However, pilot work using Ø2.5cm and Ø3.2cm round electrodes found that these caused greater discomfort directly underneath the electrode. Refinement of the stimulation profile (i.e. ramping) may improve comfort sufficiently to enable the use of a smaller cathodal electrode, and subsequently lead to further improvements in comfort. Some participants reported a sensation at the back of the throat during stimulation, which was possibly due to contraction of neck muscles and/or the stimulation of afferent pathways. Identification of the cause of this will require further investigation.

The stimulation did not lead to overt movements in the arm or hand in this study, and therefore, using the parameters reported here, it would not be useful as a direct substitution for FES. It is proposed that tSCS could be utilised in paired associative stimulation (PAS) plasticity protocols [43], or to alter the threshold and excitability of spinal pathways during training tasks either with or without FES. An example of the latter was recently demonstrated using epidural SCS, which was combined with long-term locomotion training, and reportedly lead to improvements in function [51]. Changes in neural plasticity in the motor system could be tested using methods similar to those described in Chapter 5, or with other techniques such as H-reflex [176] and twitch interpolation [177]. This could firstly be trailed in healthy able-bodied volunteers, before moving to groups with neurological conditions.

Finally, it should be noted that the majority of participants in this study worked in motor research, and it is anticipated that there might be a different perception of comfort outside the research setting. Further studies are required in healthy able-bodied volunteers to develop our

understanding parameters such as ramping and stimulation duration. It is recommended that where possible, these future studies operate at the lower end of the amplitude, frequency and duration values reported here.

6.4.2 Oscillatory responses

6.4.2.1 *What are the possible sources of the oscillatory responses?*

An unexpected oscillatory behaviour was observed during stimulation at 20, 50 and 100Hz (Figure 6-10, Figure 6-11, and Figure 6-12). It had been anticipated that stimulation would drive motor responses at the stimulation rate, i.e. 20, 50 or 100Hz, as the relative refractory period for median nerve and thenar muscles has been reported to be 5ms [178], suggesting firing rates of approximately 200Hz are possible. However, instead, bursts of firing at approximately 8 to 12Hz were observed, and this was consistent despite the stimulation rate being increased from 20 to 100Hz.

The source of the oscillatory behaviour is unknown, but frequencies in the region of 10Hz have been widely reported in the motor system and ascribed to a number of factors: oscillatory activity in the central nervous system, motor unit firing properties, and mechanical and reflex loop resonances [179, 180]. This section looks at the evidence collected in this study, and endeavours to elucidate the most likely driver of these responses.

6.4.2.2 *Efferent pathways*

The most distal elements in the motor system are the muscle and the neuromuscular junction (NMJ). In a control study, peripheral nerve stimulation (PNS) elicited a 10Hz oscillation (Figure 6-16), and as this will have directly stimulated efferent pathways, it could be evidence that the source of oscillations was distal to the spinal cord. However, as the number of responses per oscillation was observed to increase with frequency (see Figure 6-11), this suggests a waxing and waning control system, which would require more complex networks than are anticipated to exist at the NMJ. Furthermore, as mentioned above, the relative refractory period for median nerve and thenar muscles has been reported to be 5ms [178] and therefore, responses at higher frequencies would be anticipated. PNS will also stimulate afferent pathways, so the motor response from this stimulation may also exhibit the properties of other elements of the motor system.

Similarly, if we consider this to simply be the property of a motor neuron located in the spinal cord, we cannot explain the waxing and waning responses observed in Figure 6-12. Instead,

we might anticipate a single response followed by a period of slow hyperpolarisation, similar to that observed at 10 and 20Hz (Figure 6-11). Instead, increased firing within oscillations at 50 and 100Hz was observed. Motor units have been reported to fire doublets, with triplets much rarer, at feasible inter-spike intervals for this protocol [181]. However, it is not clear that this is what is being observed here, and some trains appear to contain 4-peaks (Figure 6-12). Researchers have previously shown that when the ventral spinal cord surface is directly stimulated (i.e. likely efferent pathways), motor responses at 100Hz are recorded, and do not show the 10Hz oscillatory behaviour described here [182]. The evidence shown here, is indicative of a more complex mechanism that is either internal to the spinal cord or the networks that interacts with it.

It should be noted that with sufficiently high currents, tSCS may directly stimulate efferent (ventral) pathways [101]. This might account for the drop-off in oscillatory behaviour observed at higher intensities (Figure 6-14-A inset) [101]. Alternatively, it could be that the merging of several oscillatory responses at various frequencies around 10Hz (e.g. Figure 6-10-A) leads to the reduction in 10Hz power. Finally, a 100Hz 0.5s stimulus train with Poisson firing (Figure 6-18), showed similar oscillatory behaviour with a peak around 12Hz, which provides evidence that the oscillations are not a special property of stimulation delivered with a consistent inter-stimulus interval.

6.4.2.3 *Central pattern generators (CPGs)*

Researchers have reported that transcutaneous and epidural SCS stimulation can be used to drive central pattern generators (CPGs) located in the lumbar spinal cord which are associated with the lower limb. The motor output of these CPGs also forms a modulating envelope, but there is little to no evidence of CPGs for the upper limb in humans. Furthermore, investigation of the responses recorded here, found that oscillations simultaneously occurred at different frequencies in different muscles (Figure 6-15), and possibly within the same muscle (Figure 6-10). This is contrary to the idea of a CPG that might be anticipated to keep oscillations in synchrony. Synchronous oscillations were also observed in agonist / antagonist muscle pairings, i.e. EDC and FDS (Figure 6-12), which could be considered contrary to the firing of a CPG, as depending on the movement, it might be expected to inhibit the antagonist muscle when activating the agonist.

6.4.2.4 *Dorsal roots, peripheral nerves and intrinsic oscillators*

Transcutaneous SCS has been shown by Minassian et al. to stimulate afferent pathways, believed to be group Ia afferents located in the dorsal roots, to elicit posterior root-muscle reflexes [101]. A large fibre diameter, location in the root, fibre curvature and a relatively low threshold, are all cited as possible reasons for this bias towards group Ia afferents over other sensory fibres. Minassian et al. also showed that following a first stimulus, a second stimulus 50ms later, would elicit either no response or a response with a reduced amplitude [101]. They suggested that this refractory period was evidence that responses were produced by afferent reflex pathways, rather than direct activation of motor neurons. Indeed, this 50ms window is in agreement with the responses reported here, but we are additionally showing bursts of oscillatory activity, which suggests a more complex mechanism than a simple refractory window. Similar 10Hz oscillations have been noted during epidural stimulation of the non-human primate spinal cord [183], which as noted by Minassian et al., may stimulate the dorsal roots via the cerebrospinal fluid, rather than directly stimulating neurons located in the spinal cord [101]. Investigators have shown that similar neural structures are likely stimulated by both transcutaneous and epidural SCS [58]. Interestingly, group Ia fibres are the sensory fibres for muscle spindles, and muscle spindle feedback has been associated with neuroplasticity and function recovery in a mouse SCI model [184, 185].

Ten hertz dorsal root potentials have been recorded from the lumbar spinal cord in anaesthetised rats [186]. Here, the authors concluded that the isolated cord contained a synchronous oscillatory mechanism at approximately 10Hz which was inhibited by impulses in the dorsolateral funiculus and synchronised by intrinsic axons in the Lissauer tract. Both of which lie in close proximity to the dorsal roots. Similarly, a spinally mediated 10Hz rhythm has been recorded in sympathetic nerve activity in cats following electrical stimulation of the dorsolateral funiculus, with the spinal cord and peripheral nerves suggested as a possible source [187]. These studies both provide evidence for the possible existence of intrinsic oscillators within the spinal cord, and the latter, a possible peripheral nerve component.

Oscillations at frequencies around 10Hz are a prominent feature of muscle spasms or clonus following SCI [188, 189], with the EMG pattern described as consisting of “packets” of activity [190], which is an apt description of the oscillations observed here (Figure 6-10, Figure 6-11, and Figure 6-12). It has been proposed that since spinal cord lesions interrupt supraspinal connections, the most likely source of these spasms is the spinal cord and its peripheral feedback loops [189]. A leading view was that recurrent activation of stretch reflexes caused

this clonus, as evidence suggested the frequency of clonus correlated with reflex path length [190, 191]. However, more recent research suggest that clonus may be caused by an interaction of central mechanisms and peripheral events [190, 192]. Interestingly, as early as the 1980s, SCS has been linked to reduction in clonus in people with multiple sclerosis [193], and more recently, the control of spasticity following SCI [194], where it was noted the frequency of stimulation must be in the range of 50 to 100 Hz to be effective.

A possible explanation for the different oscillation frequencies between and within muscles (see Figure 6-10 and Figure 6-15), is that additional central delays are caused by activation of propriospinal-like (non-monosynaptic) pathways [195], or as stimulation is located over the C7 vertebrae, and therefore likely disproportionately targeting C7 and C8 neurological levels, the differences could be accounted for by delays between segmental layers.

6.4.2.5 Cortical input

Studies have shown that recordings from both the cortex and periphery contain signals with a strong 10Hz component, but the lack of corticomuscular coherence at 10Hz is of note [196]. Williams et al. proposed that spinal interneuronal circuits may have the capacity to reduce 10Hz cortical inputs through phase cancellation, and a component of this may be mediated by Renshaw Cells acting through recurrent inhibition [197, 198]. It is possible that tSCS is disrupting this system, and this results in the oscillations observed here. However, it was shown that a gentle voluntary contraction (see Figure 6-17) can also produce an oscillatory response, and it seems likely that near motor threshold tSCS is replicating this, rather than interfering with an on-going phase cancellation. Furthermore, it does not seem likely that the drop-off in 10Hz power at higher frequencies (Figure 6-4-A), is caused by the late activation of a phase cancellation system. Nevertheless, Renshaw cells may be a possible intrinsic oscillator that could modulate the output of motoneurons, although researchers have questioned whether Renshaw cells are present in distal upper limb muscles [192, 199, 200]. Either way, intrinsic oscillators that act locally (rather than globally, like a CPG) on either a single or group of motor units, and receive input from afferent fibres, seem a credible explanation for the effects observed here.

6.4.2.6 Summary

By introducing an external stimulus to the motor system, possibly through Ia afferents in the dorsal spinal roots, it appears that we are replicating a gentle tonic input (similar to that shown in Figure 6-17) which evokes a response in a small number of motor units. The response occurs

at 10Hz as the motor system has an intrinsic tendency through intraspinal networks and reflex loops to respond at this frequency [179, 180], which may be a beneficial property of the motor system, as it restricts the continuous firing of individual motor neurons that could lead to fatigue. As the intensity of stimulation is increased, this clear 10Hz oscillation reduces as further motor units are recruited at range of frequencies around 10Hz. To explore this further, in addition to a larger dataset, the importance of reflex loops could be tested either by: eliciting oscillations in the lower limb, cooling of the upper limb to reduce conduction times, or tendon vibration [101].

Following suitable further testing, tSCS may enable the modulation of hyper-excitability reflex pathways [17, 162] and intramuscular coherence which have been associated with clonus and spasticity in SCI [201]. Furthermore, if propriospinal pathways are being activated, modulation of this system could be explored for reducing motor deficits that lead to problems such as trips and falls in some neurological conditions [202]. The 10Hz response suggests that intrinsic pathways for motor unit recruitment are being activated, which could offer advantages over stimulation that targets efferent pathways (e.g. ventral SCS, PNS and FES) as it may reduce muscle fatigue and promote natural recruitment of muscle fibres, although it does not offer selectivity of muscles. Therefore, tSCS may provide an important pathway for manipulating the motor system for therapeutic applications, and could also have a role in the diagnosis of neurological conditions where oscillations may be impaired.

6.5 Conclusion

In a small sample of healthy able-bodied volunteers, high frequency bursts of transcutaneous spinal cord stimulation (tSCS) have been shown to be significantly more comfortable than stimulation protocols that use a single stimulus, when compared at 110% of the resting motor threshold for each stimulation type. While reported differences in comfort were small, this might be improved through refinement of parameters such as the number of stimuli contained within a burst and the use ‘ramping’.

Oscillations at approximately 10Hz were observed in EMG signals when stimulation was delivered between 20 and 100Hz. These responses were intermittently observed across all muscles and participants, particularly at higher intensities and frequencies of stimulation, although a drop-off at the highest intensities was also observed. It is proposed that these oscillations may be caused by the activation of spinal networks and reflex pathways which have an intrinsic propensity to respond at 10Hz. While further research must be conducted to

understand the underlying mechanisms and the safety of interventions, tSCS could have important applications in the treatment of spasticity and clonus, as it may allow the activation and manipulation of spinal networks in a manner not accessible by other forms of stimulation.

Furthermore, while not a direct substitute for FES, tSCS could be utilised in paired associative stimulation (PAS) plasticity protocols and to alter spinal cord excitability in neurological conditions that lead motor impairment. These protocols could subsequently be integrated into closed-loop rehabilitative devices such as the one developed in this thesis, or novel wearable devices.

Chapter 7

General discussion: A novel
approach to upper limb
rehabilitation following spinal cord
injury and stroke

7.1 Overview

There is a world-wide demand for effective interventions to improve upper limb outcomes following neurological conditions such as stroke and spinal cord injury (SCI). While evidence for current interventions is limited, an understanding of the role of associative learning and neural plasticity during recovery is emerging from the field of neuroscience. In this thesis, a novel device to manipulate and enhance this recovery process was developed. The device paired voluntary brain activity with stimulation to the peripheral motor system to facilitate the completion of a reaching and grasping task, and sought to improve function through Hebbian plasticity mechanisms. Furthermore, the device was designed to overcome common barriers to translation from the laboratory to the clinic: cost, robustness, adaptability and ease of independent use.

It was demonstrated in a series of feasibility studies that following a short intervention, selected stroke survivors and selected individuals with SCI were able to use the device and gave positive feedback. Furthermore, some participants made modest gains on an object manipulation task, and a subsequent study showed that stroke survivors may continue to make gains with longer periods of training.

These studies added to a growing body of evidence that following stroke, and the closing of the ‘critical window’ [27], at least modest functional gains are possible [29, 30] and that these changes may be sustained for at least a short period following the completion of an intervention. While the modest improvements shown were promising, it is clearly desirable to optimise interventions to maximise functional gains. To this end, and to understand how the device might be acting on the motor system, a transcranial magnetic stimulation (TMS) study was conducted in healthy abled-bodied volunteers to measure changes in corticospinal excitability following a short intervention with device. Importantly, facilitation was only observed in the antagonist flexor muscle, and this facilitation could be increased by adjusting the relative timing of the cue and stimulation onset, to theoretically converge the ascending and descending signals in the spinal cord. Differences were also found between conditions in which stimulation was delivered concurrent with movement and alternatively, during a rest period between voluntary movements, suggesting different mechanisms of action, which might be important in a rehabilitative setting.

The findings of this study were contrary to the original hypothesis that the stimulated muscle (EDC) would be facilitated following an intervention with the device, and evidence that the mechanisms of action of paired associative stimulation (PAS) plasticity protocols still need to be fully understood. The study has added further evidence to a growing consensus that an extensor / flexor bias exists in the motor system, and that the outcomes of studies such as this must be interpreted with care. It is unknown how these results in healthy able-bodied volunteers would translate to stroke survivors and participants with SCI, but the amplitude of motor evoked potentials and the resting motor threshold found using TMS, have both been correlated with spasticity in the hand and other motor function measures following stroke [164].

It is important that interventions are optimised and shown to produce consistent results as larger trials should be considered as ‘one-shot’ endeavours. A negative result means that further funding is unlikely, especially for changes in the protocol that would be perceived as minor, such as the refinement of the stimulation onset time. Furthermore, if small changes can improve the efficacy of an intervention, there are important consequences for cost, participant uptake and sustainability of the therapy. This is a sentiment echoed in the Medical Research Council guidelines on ‘Developing and evaluating complex interventions’ [203]. It states that there is a *‘need for greater investment in developmental studies prior to large scale evaluations’* and emphasises the need for an intervention to have coherent theoretical basis before proceeding to a large-scale evaluation. While the intervention developed in this thesis has a good theoretical basis, it has become apparent that further studies are required to develop our understanding of neural plasticity in both the healthy and impaired motor system.

Finally, this thesis explored a novel stimulation technique: transcutaneous spinal cord stimulation (tSCS). It was demonstrated that responses could be evoked in the upper limb using trains of stimuli that were within reasonable comfort levels for healthy able-bodied volunteers, and that at 110% of resting motor threshold for each stimulation type, high frequency bursts of stimuli may be more comfortable than a single stimulus. As responses did not lead to overt movements of the hand or arm, for the parameters tested, tSCS is not suitable as a direct substitution for functional electrical stimulation (FES). An unexpected ~10Hz oscillation was observed in motor responses, and this provided insights into which neural structures may be activated by tSCS. While further work is required to characterise and understand the safe application of this technique, it might enable the activation of spinal and reflex pathways in an alternative manner to other stimulation techniques, and provide a new method of manipulating neural plasticity, in particular, for the treatment of clonus and spasticity.

7.2 Translational pipeline

The translation of basic science into the health service is coming under increasing scrutiny [204-206]. Classically, the translation pipeline is divided into unidirectional steps: Type 1 and Type 2, with Type 1 making the link between basic science and clinical trials, and Type 2, the subsequent move into health service research and delivery [205]. However, for complex conditions such as stroke, there are now calls for new bidirectional approaches, in particular to overcome the divide between basic scientists, clinicians and user-groups [205].

Further to this, healthcare technology is covered by rigorous regulatory frameworks, and the translation of any device out of the laboratory is subject to stringent checks. While important for consumer protection, these regulations are felt by some to be particularly detrimental for devices that target a relatively small number of people, such as bladder control following SCI [207], and likely exacerbates a gap between academia and industry. Hansjörg Wyss, the philanthropist behind the Harvard University's Wyss Institute for Biologically Inspired Engineering, points out that while academics do not suffer from industry's aversion to risk, they primarily "*publish papers and make widgets*" [208].

More fundamental changes to the wider research environment are required to overcome challenges in the translational pipeline. This could be driven by philanthropists such as Hansjörg Wyss, or through empowerment of funding-bodies that represent user-groups. For example, charities and not-for-profit organisations such as Wings for Life [209], Aspire [210] and Stroke Association [211], who have a remit to ensure that research reaches further than the next academic publication. However, to influence national and international policy, large funding bodies such the Wellcome Trust [212] will have to be engaged. Furthermore, research centres should be encouraged to not only integrate medical sciences and engineering, but also social scientists with expertise in policy.

This thesis has tried to overcome many of these obstacles to Type 1 translation, for example, by employing a simple and robust design, involving clinicians and user-groups, using existing non-invasive techniques, and targeting the large number of people effected by stroke. Nevertheless, it is likely that significant changes to the design will be required before it can be translated outside the laboratory for further evaluation, and later, for possible commercialisation. Here, a partnership with industry may be beneficial, although concerns over intellectual property could take precedence over the needs of the end-user.

Once developed, the system described in thesis would meet many of the criteria discussed in the literature [73] and the introduction to this thesis. For example, Mann et al. highlighted the need for a triggering device to allow participants to receive FES whilst completing functional tasks [80]. The device would also be suitable for use across a number of study centres, and its simple operation would be favourable in trials without technical support. This would allow the promising results shown in this thesis to be tested further. It is also anticipated the device would be available at relatively low-cost. Nevertheless, data presented in this thesis indicates that the device, in its present form, would only be suitable for a sub-population of stroke-survivors and people with SCI. For that reason, it is envisaged that the developed system would be a valuable addition to a therapists 'toolbox', to be used when appropriate for a particular individual. The feedback from the physiotherapist focus group in Chapter 2, suggested that the device would be met with a positive reception by this potential user-group.

In recent decades, technology and our understanding of neuroscience have made significant advances, but the translational environment needs to keep pace. While it is the responsibility of scientists and engineers to remain focused beyond the first publication, to avoid overstating their findings, and to work with clinicians, commercial partners and social scientists, this effort must be supported by funding bodies and research institute management who are able to create an environment that enables this. They must recognise that there is a *'need for greater investment in developmental studies prior to large scale evaluations'* [203], and provide researchers with the job security and continuity required to complete thorough developmental studies, allowing time to refine, optimise and understand new technology.

7.3 A closed loop?

In traditional engineering disciplines, a closed-loop does not take input from a human operator, but of course, this definition is redundant for a neural interface which must interface with a human (or animal). Jackson and Zimmerman [24] described a bi-directional coupling between the nervous system and neuroelectronics which allows information to travel in a 'closed-loop'. They went on to outline a system which decodes neural signals to control an effector which in turn gives feedback to the user, typically through visual feedback, although afferent feedback could be used. This type of brain-machine interface (BMI) will typically record neuronal information and convert it into actions via external software or hardware, and can be considered to be 'brain-led'. That is, the loop is initiated by a neural commands or signals generated by the brain which are then sensed by the machine.

However, this approach, as well as other approaches that try to record or infer brain activity via artificial means, neglect that sensory pathways such as vision, touch and sound, are used by computers to interact with the central and peripheral nervous system on a daily basis. There was a clear opportunity to exploit this existing biological machinery, to create a ‘machine-led’ closed loop.

This approach is now being adopted by researchers such as Foysal et al. [151] who used a non-invasive auditory stimulus to activate reticulospinal pathways. They pair this activation with peripheral nerve stimulation (in an open loop) to induce plasticity, which they believe may be beneficial for stroke survivors. This device can be considered ‘machine-led’, as it is the machine, via an auditory stimulus, that initiates and drives the loop through an in-built knowledge of sensory processing by the brain. Rather than the machine sensing the brain, the brain senses the machine.

The same approach is utilised in this thesis. The device forms a closed-loop with the user, but in contrast to conventional BCIs or closed-loop systems, it uses knowledge of how a trained human brain will react to a sensory stimulus (i.e. a cue or a command) to deliver appropriately timed stimulation. More traditional means are employed to cease stimulation at the end of the movement, i.e. the detection of movement, which is more commonly accepted as being part of a closed-loop system [76].

It is predicted that as artificial intelligence and our understanding of the brain and nervous system advances, ‘machine-led’ closed-loops that manipulate how the brain and nervous system will react to different stimuli or inputs will become more prevalent in the field of neural prostheses.

7.4 The future of FES

While the origins of electrical stimulation can be traced back much further, feasibility studies of novel FES devices have been conducted since the 1970s. In 1975, Merletti and colleagues designed an upper limb FES orthosis, and reported significant functional rehabilitation of hemiplegic participants [213]. They proposed that an extensive clinical evaluation program was justified. Numerous devices have since been developed [65, 214], and with the modernisation and miniaturisation of electronics, and an improved understanding of neuroscience [24], 2018 has been described as a ‘critical time’ for engineered neuroplasticity

[215]. However, with over 40 years since these pioneering FES studies, should we be worried that FES simply is not good enough?

Unfortunately there is a common theme, both the 2014 Cochrane Review [11] ('Cochrane overview: Interventions for improving upper limb function after stroke') and a recent systematic review with meta-analysis by Eraifej et al. [79] point to the lack of high quality evidence for FES based interventions following stroke. This is likely because many studies stop after small pilot and feasibility studies, and simply conclude that further studies should be undertaken, without taking this next step. There are many reasons for this, large clinical trials are expensive and challenging to run, and it is likely that many prototype devices do not offer the flexibility required for clinical practice, and require on-going engineering support. Other groups have indeed taken the next step, but only to find a negative result [216, 217].

To counter this challenge, a collaboration including The National Clinical FES Centre, devised the FES-UPP device [73]. It was specifically designed for therapists with little or no FES or programming experience, and uses inertial measurement units (IMU) to track a participant's movement, applying stimulation at the correct time. Alongside this thesis, the FES-UPP device shows a convergence in the field, recognising that devices not only need to provide electrical stimulation at an appropriate time, but must be user friendly, flexible and suitable for the clinic.

The element of doubt surrounding FES led therapies suggests that outcomes are either inconsistent, too slow to show improvements, plateau, not substantially better than alternatives, or that evidence of effectiveness is lacking [11, 218, 219]. This might be countered by refining stimulation, treatment and evaluation protocols, and by developing an understanding of the theoretical basis of the intervention prior to larger studies. Furthermore, recruitment needs to be informed by an appreciation of who might respond to the treatment, i.e. a-priori classification of likely 'responders' and likely 'non-responders'. In addition to functional assessments, this could be achieved by neuroimaging and modelling studies that predict recovery outcomes [28].

It is important that research groups do not rush towards large scale evaluation of devices, but take the time required to understand the underlying mechanisms, and refine and optimise treatment and stimulation protocols, recognising under what circumstances they may be effective.

7.5 Further studies

The conclusion of this thesis should not simply be that a larger study is required. The device should continue to be developed ensuring that it is safe, adaptable, easy-to-use and modular, but further to this, studies should be completed to understand the mechanism of action, and how the intervention can be refined.

To this end, studies in healthy able-bodied volunteers should be conducted to confirm the additional facilitation brought about by the optimised stimulation timing, and whether this can be further enhanced. Separate studies should then be conducted with stroke survivors and individuals with SCI, to confirm if the results are replicated in these groups. In stroke survivors, this could be conducted using the affected and unaffected limb, providing a natural control. The output of these studies, and any subsequent studies, would be used to produce an optimised intervention protocol with an identified mechanism of action.

To investigate a possible extensor / flexor bias within the motor system, a review of upper and lower limb plasticity studies should be conducted, with a focus on: which muscles were stimulated, whether a facilitation or suppression was observed, and if the stimulation was paired with cortical activity. This will help the scientific community to understand and interpret the outcomes of these studies, and how they might translate to a rehabilitative setting.

A paired associative stimulation (PAS) study in healthy able-bodied volunteers using tSCS, similar to that shown in animal models [174], would demonstrate whether this technique has the potential to facilitate descending commands. Furthermore, the oscillatory response should be further characterised, and bursts of stimulation optimised to enhance comfort. If shown to have potential therapeutic benefits, integration of the technology into a wearable device would be valuable engineering endeavour.

The studies in this thesis have focused on chronic stroke and SCI (>6 months from injury). This was due to limited access to acute and sub-acute groups, and because natural recovery is believed to have plateaued during the chronic phase. While evidence has suggested that recovery is possible following the closing of the ‘critical window’, the importance of early intervention cannot be ignored. Following appropriate planning, it would be of interest to test the device in a sub-acute population. Use of the device, and subsequent use of the trained limb for activities of daily living, could be monitored using an activity watch, such as that reported by Da-Silva et al. [220].

7.6 Summary

Global improvements in medicine mean that the non-fatal dimensions of disease and injury will become an increasing burden on healthcare systems world-wide [2]. This will lead to an increased emphasis on rehabilitation, which will require innovative therapeutic strategies. With regards to this, the scientific community has reasons to be optimistic. Our knowledge of the human body has never been greater, and advances in the capability and availability of technology provides the tools and techniques necessary for exploiting this improved understanding. The closed-loop device developed in this thesis is an important step towards a novel solution for upper limb rehabilitation following stroke and SCI, but it is not the finished article. This thesis has highlighted gaps in our knowledge of how the motor system works, and how stimulation techniques interact with it. Progress will be made, but the pace of this is dependent on the ability of the research community to create a supportive, stable and inter-disciplinary environment, in which new technologies with a comprehensive theoretical basis can be developed.

References

- [1] E. F. Hodkin, Y. Lei, J. Humby, I. S. Glover, S. Choudhury, H. Kumar, M. A. Perez, H. Rodgers, and A. Jackson, "Automated FES for upper limb rehabilitation following stroke and spinal cord injury," *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 26, no. 5, pp. 1067-1074, 2018.
- [2] Global Burden of Disease Study 2016, "Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016," *Lancet*, vol. 390, no. 10100, pp. 1211-1259, Sep 16, 2017.
- [3] A. Singh, L. Tetreault, S. Kalsi-Ryan, A. Nouri, and M. G. Fehlings, "Global prevalence and incidence of traumatic spinal cord injury," *Clinical Epidemiology*, vol. 6, pp. 309-331, 09/23, 2014.
- [4] B. B. Lee, R. A. Cripps, M. Fitzharris, and P. C. Wing, "The global map for traumatic spinal cord injury epidemiology: update 2011, global incidence rate," *Spinal Cord*, vol. 52, pp. 110, 02/26/online, 2013.
- [5] A. S. Go, D. Mozaffarian, V. L. Roger, E. J. Benjamin, J. D. Berry, W. B. Borden, D. M. Bravata, S. Dai, E. S. Ford, C. S. Fox, S. Franco, H. J. Fullerton, C. Gillespie, S. M. Hailpern, J. A. Heit, V. J. Howard, M. D. Huffman, B. M. Kissela, S. J. Kittner, D. T. Lackland, J. H. Lichtman, L. D. Lisabeth, D. Magid, G. M. Marcus, A. Marelli, D. B. Matchar, D. K. McGuire, E. R. Mohler, C. S. Moy, M. E. Mussolino, G. Nichol, N. P. Paynter, P. J. Schreiner, P. D. Sorlie, J. Stein, T. N. Turan, S. S. Virani, N. D. Wong, D. Woo, and M. B. Turner, "Heart disease and stroke statistics—2013 Update: A report from the American Heart Association," *Circulation*, vol. 127, no. 1, pp. e6-e245, January 1, 2013, 2013.
- [6] Stroke Association, "State of the nation: Stroke statistics - February 2018," https://www.stroke.org.uk/system/files/sotn_2018.pdf [Accessed 27 September 2018], 2018.
- [7] J. D. Pandian, and P. Sudhan, "Stroke epidemiology and stroke care services in India," *Journal of Stroke*, vol. 15, no. 3, pp. 128-134, 2013.
- [8] E. S. Lawrence, C. Coshall, R. Dundas, J. Stewart, A. G. Rudd, R. Howard, and C. D. Wolfe, "Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population," *Stroke*, vol. 32, no. 6, pp. 1279-84, Jun, 2001.
- [9] A. K. Welmer, L. W. Holmqvist, and D. K. Sommerfeld, "Limited fine hand use after stroke and its association with other disabilities," *J Rehabil Med*, vol. 40, no. 8, pp. 603-8, Aug, 2008.
- [10] A. Pollock, B. St George, M. Fenton, and L. Firkins, "Top 10 research priorities relating to life after stroke--consensus from stroke survivors, caregivers, and health professionals," *Int J Stroke*, vol. 9, no. 3, pp. 313-20, Apr, 2014.
- [11] A. Pollock, S. E. Farmer, M. C. Brady, P. Langhorne, G. E. Mead, J. Mehrholz, and F. van Wijck, "Cochrane overview: Interventions for improving upper limb function after stroke," *Stroke*, vol. 46, no. 3, pp. e57-e58, March 1, 2015, 2015.
- [12] Royal College of Physicians, British Society of Rehabilitation Medicine, Multidisciplinary Association of Spinal Cord Injury Professionals, British Association of Spinal Cord Injury Specialists, and Spinal Injuries Association, "Chronic spinal cord injury: management of patients in acute hospital settings: national guidelines. ," *Concise Guidance to Good Practice series No 9*, RCP, 2008.
- [13] The National Spinal Cord Injury Statistical Center (NSCISC), "Spinal Cord Injury (SCI) 2016 Facts and Figures at a Glance," *J Spinal Cord Med*, vol. 39, no. 4, pp. 493-4, Jul, 2016.
- [14] K. D. Anderson, "Targeting recovery: priorities of the spinal cord-injured population," *J Neurotrauma*, vol. 21, no. 10, pp. 1371-83, Oct, 2004.
- [15] K. Nas, L. Yazmalar, V. Şah, A. Aydın, and K. Öneş, "Rehabilitation of spinal cord injuries," *World Journal of Orthopedics*, vol. 6, no. 1, pp. 8-16, 2015.

- [16] S. C. Kirshblum, S. P. Burns, F. Biering-Sorensen, W. Donovan, D. E. Graves, A. Jha, M. Johansen, L. Jones, A. Krassioukov, M. Mulcahey, M. Schmidt-Read, and W. Waring, "International standards for neurological classification of spinal cord injury (Revised 2011)," *J Spinal Cord Med*, vol. 34, no. 6, pp. 535-46, Nov, 2011.
- [17] C. Trompetto, L. Marinelli, L. Mori, E. Pelosin, A. Currà, L. Molfetta, and G. Abbruzzese, "Pathophysiology of spasticity: Implications for neurorehabilitation," *BioMed Research International*, vol. 2014, pp. 8, 2014.
- [18] J. Long, P. Federico, and M. A. Perez, "A novel cortical target to enhance hand motor output in humans with spinal cord injury," *Brain*, vol. 140, no. 6, pp. 1619-1632, 2017.
- [19] H. Y. Jung, J. Lee, and H. I. Shin, "The natural course of passive tenodesis grip in individuals with spinal cord injury with preserved wrist extension power but paralyzed fingers and thumbs," *Spinal Cord*, vol. 56, no. 9, pp. 900-906, Sep, 2018.
- [20] V. Dietz, and K. Fouad, "Restoration of sensorimotor functions after spinal cord injury," *Brain*, vol. 137, no. 3, pp. 654-667, 2014.
- [21] J. W. McDonald, and C. Sadowsky, "Spinal-cord injury," *The Lancet*, vol. 359, no. 9304, pp. 417-425, 2002/02/02/, 2002.
- [22] E. S. Stauffer, "Neurologic recovery following injuries to the cervical spinal cord and nerve roots," *Spine*, vol. 9, no. 5, pp. 532-4, Jul-Aug, 1984.
- [23] J. G. McPherson, R. R. Miller, and S. I. Perlmutter, "Targeted, activity-dependent spinal stimulation produces long-lasting motor recovery in chronic cervical spinal cord injury," *Proc Natl Acad Sci U S A*, vol. 112, no. 39, pp. 12193-8, Sep 29, 2015.
- [24] A. Jackson, and J. B. Zimmermann, "Neural interfaces for the brain and spinal cord--restoring motor function," *Nat Rev Neurol*, vol. 8, no. 12, pp. 690-9, Dec, 2012.
- [25] V. Dietz, "Improving outcome of sensorimotor functions after traumatic spinal cord injury," *F1000Research*, vol. 5, 2016.
- [26] J. Bernhardt, K. S. Hayward, G. Kwakkel, N. S. Ward, S. L. Wolf, K. Borschmann, J. W. Krakauer, L. A. Boyd, S. T. Carmichael, D. Corbett, and S. C. Cramer, "Agreed definitions and a shared vision for new standards in stroke recovery research: The Stroke Recovery and Rehabilitation Roundtable taskforce," *International Journal of Stroke*, vol. 12, no. 5, pp. 444-450, 2017/07/01, 2017.
- [27] H. Nakayama, H. S. Jorgensen, H. O. Raaschou, and T. S. Olsen, "Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study," *Arch Phys Med Rehabil*, vol. 75, no. 4, pp. 394-8, Apr, 1994.
- [28] N. S. Ward, "Restoring brain function after stroke - bridging the gap between animals and humans," *Nat Rev Neurol*, vol. 13, no. 4, pp. 244-255, Apr, 2017.
- [29] J. McCabe, M. Monkiewicz, J. Holcomb, S. Pundik, and J. J. Daly, "Comparison of robotics, functional electrical stimulation, and motor learning methods for treatment of persistent upper extremity dysfunction after stroke: a randomized controlled trial," *Arch Phys Med Rehabil*, vol. 96, no. 6, pp. 981-90, Jun, 2015.
- [30] C. E. Lang, K. R. Lohse, and R. L. Birkenmeier, "Dose and timing in neurorehabilitation: prescribing motor therapy after stroke," *Curr Opin Neurol*, vol. 28, no. 6, pp. 549-55, Dec, 2015.
- [31] J. A. Kleim, and T. A. Jones, "Principles of experience-dependent neural plasticity: Implications for rehabilitation after brain damage," *Journal of Speech, Language, and Hearing Research*, vol. 51, no. 1, pp. S225-S239, 2008.
- [32] J. Classen, J. Liepert, S. P. Wise, M. Hallett, and L. G. Cohen, "Rapid plasticity of human cortical movement representation induced by practice," *J Neurophysiol*, vol. 79, no. 2, pp. 1117-23, Feb, 1998.
- [33] L. Wang, J. M. Conner, A. H. Nagahara, and M. H. Tuszynski, "Rehabilitation drives enhancement of neuronal structure in functionally relevant neuronal subsets," *Proceedings of the National Academy of Sciences*, February 22, 2016, 2016.

- [34] C. E. Lang, J. R. Macdonald, D. S. Reisman, L. Boyd, T. Jacobson Kimberley, S. M. Schindler-Ivens, T. G. Hornby, S. A. Ross, and P. L. Scheets, "Observation of amounts of movement practice provided during stroke rehabilitation," *Arch Phys Med Rehabil*, vol. 90, no. 10, pp. 1692-8, Oct, 2009.
- [35] K. S. Hayward, and S. G. Brauer, "Dose of arm activity training during acute and subacute rehabilitation post stroke: a systematic review of the literature," *Clin Rehabil*, vol. 29, no. 12, pp. 1234-43, Dec, 2015.
- [36] J. Bernhardt, H. Dewey, A. Thrift, and G. Donnan, "Inactive and alone: physical activity within the first 14 days of acute stroke unit care," *Stroke*, vol. 35, no. 4, pp. 1005-9, Apr, 2004.
- [37] J. Bernhardt, J. Chan, I. Nicola, and J. M. Collier, "Little therapy, little physical activity: rehabilitation within the first 14 days of organized stroke unit care," *J Rehabil Med*, vol. 39, no. 1, pp. 43-8, Jan, 2007.
- [38] J. W. Rowland, G. W. J. Hawryluk, B. Kwon, and M. G. Fehlings, "Current status of acute spinal cord injury pathophysiology and emerging therapies: promise on the horizon," *Neurosurgical Focus*, vol. 25, no. 5, pp. E2, 2008/11/01, 2008.
- [39] R. N. Lemon, "Descending pathways in motor control," *Annual Review of Neuroscience*, vol. 31, no. 1, pp. 195-218, 2008/07/01, 2008.
- [40] E. S. Boyden, "A history of optogenetics: the development of tools for controlling brain circuits with light," *F1000 Biology Reports*, vol. 3, pp. 11, 05/03, 2011.
- [41] E. B. Plow, J. R. Carey, R. J. Nudo, and A. Pascual-Leone, "Invasive cortical stimulation to promote recovery of function after stroke: a critical appraisal," *Stroke*, vol. 40, no. 5, pp. 1926-31, May, 2009.
- [42] M. Kobayashi, and A. Pascual-Leone, "Transcranial magnetic stimulation in neurology," *Lancet Neurol*, vol. 2, no. 3, pp. 145-56, Mar, 2003.
- [43] A. Suppa, A. Quartarone, H. Siebner, R. Chen, V. Di Lazzaro, P. Del Giudice, W. Paulus, J. C. Rothwell, U. Ziemann, and J. Classen, "The associative brain at work: Evidence from paired associative stimulation studies in humans," *Clin Neurophysiol*, vol. 128, no. 11, pp. 2140-2164, Nov, 2017.
- [44] P. M. Rossini, D. Burke, R. Chen, L. G. Cohen, Z. Daskalakis, R. Di Iorio, V. Di Lazzaro, F. Ferreri, P. B. Fitzgerald, M. S. George, M. Hallett, J. P. Lefaucheur, B. Langguth, H. Matsumoto, C. Miniussi, M. A. Nitsche, A. Pascual-Leone, W. Paulus, S. Rossi, J. C. Rothwell, H. R. Siebner, Y. Ugawa, V. Walsh, and U. Ziemann, "Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee," *Clin Neurophysiol*, vol. 126, no. 6, pp. 1071-107, Jun, 2015.
- [45] A. R. Brunoni, M. A. Nitsche, N. Bolognini, M. Bikson, T. Wagner, L. Merabet, D. J. Edwards, A. Valero-Cabre, A. Rotenberg, A. Pascual-Leone, R. Ferrucci, A. Priori, P. S. Boggio, and F. Fregni, "Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions," *Brain Stimul*, vol. 5, no. 3, pp. 175-195, Jul, 2012.
- [46] S. Hesse, A. Waldner, J. Mehrholz, C. Tomelleri, M. Pohl, and C. Werner, "Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: an exploratory, randomized multicenter trial," *Neurorehabil Neural Repair*, vol. 25, no. 9, pp. 838-46, Nov-Dec, 2011.
- [47] L. Tedesco Triccas, J. H. Burridge, A. M. Hughes, K. L. Meadmore, M. Donovan-Hall, J. C. Rothwell, and G. Verheyden, "A qualitative study exploring views and experiences of people with stroke undergoing transcranial direct current stimulation and upper limb robot therapy," *Top Stroke Rehabil*, pp. 1-9, Sep 20, 2018.
- [48] K. Kumar, C. Toth, R. K. Nath, and P. Laing, "Epidural spinal cord stimulation for treatment of chronic pain--some predictors of success. A 15-year experience," *Surg Neurol*, vol. 50, no. 2, pp. 110-20; discussion 120-1, Aug, 1998.

- [49] K. Minassian, B. Jilge, F. Rattay, M. M. Pinter, H. Binder, F. Gerstenbrand, and M. R. Dimitrijevic, "Stepping-like movements in humans with complete spinal cord injury induced by epidural stimulation of the lumbar cord: electromyographic study of compound muscle action potentials," *Spinal Cord*, vol. 42, no. 7, pp. 401-16, Jul, 2004.
- [50] S. Harkema, Y. Gerasimenko, J. Hodes, J. Burdick, C. Angeli, Y. Chen, C. Ferreira, A. Willhite, E. Rejc, R. G. Grossman, and V. R. Edgerton, "Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study," *Lancet*, vol. 377, no. 9781, pp. 1938-47, Jun 4, 2011.
- [51] C. A. Angeli, M. Boakye, R. A. Morton, J. Vogt, K. Benton, Y. Chen, C. K. Ferreira, and S. J. Harkema, "Recovery of over-ground walking after chronic motor complete spinal cord injury," *New England Journal of Medicine*, vol. 379, no. 13, pp. 1244-1250, 2018/09/27, 2018.
- [52] M. Capogrosso, T. Milekovic, D. Borton, F. Wagner, E. M. Moraud, J. B. Mignardot, N. Buse, J. Gandar, Q. Barraud, D. Xing, E. Rey, S. Duis, Y. Jianzhong, W. K. Ko, Q. Li, P. Detemple, T. Denison, S. Micera, E. Bezaud, J. Bloch, and G. Courtine, "A brain-spine interface alleviating gait deficits after spinal cord injury in primates," *Nature*, vol. 539, no. 7628, pp. 284-288, Nov 10, 2016.
- [53] M. Bonizzato, G. Pidpruzhnykova, J. DiGiovanna, P. Shkorbatova, N. Pavlova, S. Micera, and G. Courtine, "Brain-controlled modulation of spinal circuits improves recovery from spinal cord injury," vol. 9, no. 1, pp. 3015, Aug 1, 2018.
- [54] S. E. Mondello, M. R. Kasten, P. J. Horner, and C. T. Moritz, "Therapeutic intraspinal stimulation to generate activity and promote long-term recovery," *Front Neurosci*, vol. 8, pp. 21, 2014.
- [55] V. K. Mushahwar, D. M. Gillard, M. J. Gauthier, and A. Prochazka, "Intraspinal micro stimulation generates locomotor-like and feedback-controlled movements," *IEEE Trans Neural Syst Rehabil Eng*, vol. 10, no. 1, pp. 68-81, Mar, 2002.
- [56] A. N. Dalrymple, D. G. Everaert, D. S. Hu, and V. K. Mushahwar, "A speed-adaptive intraspinal microstimulation controller to restore weight-bearing stepping in a spinal cord hemisection model," *J Neural Eng*, vol. 15, no. 5, pp. 056023, Oct, 2018.
- [57] Y. Gerasimenko, R. Gorodnichev, T. Moshonkina, D. Sayenko, P. Gad, and V. Reggie Edgerton, "Transcutaneous electrical spinal-cord stimulation in humans," *Ann Phys Rehabil Med*, vol. 58, no. 4, pp. 225-31, Sep, 2015.
- [58] U. S. Hofstoetter, B. Freundl, H. Binder, and K. Minassian, "Common neural structures activated by epidural and transcutaneous lumbar spinal cord stimulation: Elicitation of posterior root-muscle reflexes," *PLOS ONE*, vol. 13, no. 1, pp. e0192013, 2018.
- [59] Y. Gerasimenko, R. Gorodnichev, A. Puhov, T. Moshonkina, A. Savochin, V. Selionov, R. R. Roy, D. C. Lu, and V. R. Edgerton, "Initiation and modulation of locomotor circuitry output with multisite transcutaneous electrical stimulation of the spinal cord in noninjured humans," *J Neurophysiol*, vol. 113, no. 3, pp. 834-42, Feb 1, 2015.
- [60] F. Inanici, S. Samejima, P. Gad, V. R. Edgerton, C. P. Hofstetter, and C. T. Moritz, "Transcutaneous electrical spinal stimulation promotes long-term recovery of upper extremity function in chronic tetraplegia," *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 26, no. 6, pp. 1272-1278, 2018.
- [61] P. Gad, S. Lee, N. Terrafranca, H. Zhong, A. Turner, Y. Gerasimenko, and V. R. Edgerton, "Noninvasive activation of cervical spinal networks after severe paralysis," *J Neurotrauma*, Apr 13, 2018.
- [62] A. A. Phillips, J. W. Squair, D. G. Sayenko, V. R. Edgerton, Y. Gerasimenko, and A. V. Krassioukov, "An autonomic neuroprosthesis: noninvasive electrical spinal cord stimulation restores autonomic cardiovascular function in individuals with spinal cord injury," *J Neurotrauma*, vol. 35, no. 3, pp. 446-451, Feb 1, 2018.

- [63] P. N. Gad, E. Kreydin, H. Zhong, K. Latack, and V. R. Edgerton, "Non-invasive neuromodulation of spinal cord restores lower urinary tract function after paralysis," *Front Neurosci*, vol. 12, pp. 432, 2018.
- [64] L. Venugopalan, P. N. Taylor, J. E. Cobb, and I. D. Swain, "Upper limb functional electrical stimulation devices and their man-machine interfaces," *J Med Eng Technol*, vol. 39, no. 8, pp. 471-9, 2015.
- [65] K. Masani, and M. Popovic, "Functional electrical stimulation in rehabilitation and neurorehabilitation," *Springer Handbook of Medical Technology*, Therapeutic Devices, R. Kramme, K.-P. Hoffmann and R. S. Pozos, eds., Springer, 2011, pp. 877-896.
- [66] M. W. Keith, P. H. Peckham, G. B. Thrope, K. C. Stroh, B. Smith, J. R. Buckett, K. L. Kilgore, and J. W. Jatich, "Implantable functional neuromuscular stimulation in the tetraplegic hand," *J Hand Surg Am*, vol. 14, no. 3, pp. 524-30, May, 1989.
- [67] P. Taylor, J. Esnouf, and J. Hobby, "The functional impact of the Freehand System on tetraplegic hand function. Clinical Results," *Spinal Cord*, vol. 40, no. 11, pp. 560-6, Nov, 2002.
- [68] K. L. Kilgore, P. H. Peckham, M. W. Keith, G. B. Thrope, K. S. Wuolle, A. M. Bryden, and R. L. Hart, "An implanted upper-extremity neuroprosthesis. Follow-up of five patients," *J Bone Joint Surg Am*, vol. 79, no. 4, pp. 533-41, Apr, 1997.
- [69] K. L. Kilgore, H. A. Hoyen, A. M. Bryden, R. L. Hart, M. W. Keith, and P. H. Peckham, "An implanted upper-extremity neuroprosthesis using myoelectric control," *J Hand Surg Am*, vol. 33, no. 4, pp. 539-50, Apr, 2008.
- [70] A. B. Ajiboye, F. R. Willett, D. R. Young, W. D. Memberg, B. A. Murphy, J. P. Miller, B. L. Walter, J. A. Sweet, H. A. Hoyen, M. W. Keith, P. H. Peckham, J. D. Simeral, J. P. Donoghue, L. R. Hochberg, and R. F. Kirsch, "Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration," *The Lancet*, vol. 389, no. 10081, pp. 1821-1830, 2017.
- [71] B. C. Osuagwu, L. Wallace, M. Fraser, and A. Vuckovic, "Rehabilitation of hand in subacute tetraplegic patients based on brain computer interface and functional electrical stimulation: a randomised pilot study," *J Neural Eng*, vol. 13, no. 6, pp. 065002, Dec, 2016.
- [72] T. Yamaguchi, S. Tanabe, Y. Muraoka, S. Imai, Y. Masakado, K. Hase, A. Kimura, and M. Liu, "Effects of integrated volitional control electrical stimulation (IVES) on upper extremity function in chronic stroke," *Keio J Med*, vol. 60, no. 3, pp. 90-5, 2011.
- [73] M. Sun, C. Smith, D. Howard, L. Kenney, H. Luckie, K. Waring, P. Taylor, E. Merson, and S. Finn, "FES-UPP: A flexible functional electrical stimulation system to support upper limb functional activity practice," *Front Neurosci*, vol. 12, pp. 449, 2018.
- [74] S. C. McGie, J. Zariffa, M. R. Popovic, and M. K. Nagai, "Short-term neuroplastic effects of brain-controlled and muscle-controlled electrical stimulation," *Neuromodulation: Technology at the Neural Interface*, vol. 18, no. 3, pp. 233-240, 2015.
- [75] K. L. Meadmore, T. A. Exell, E. Hallewell, A.-M. Hughes, C. T. Freeman, M. Kutlu, V. Benson, E. Rogers, and J. H. Burridge, "The application of precisely controlled functional electrical stimulation to the shoulder, elbow and wrist for upper limb stroke rehabilitation: a feasibility study," *Journal of NeuroEngineering and Rehabilitation*, vol. 11, pp. 105-105, 2014.
- [76] D. Simonsen, E. G. Spaich, J. Hansen, and O. K. Andersen, "Design and test of a closed-loop FES system for supporting function of the hemiparetic hand based on automatic detection using the Microsoft Kinect sensor," *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 25, no. 8, pp. 1249-1256, 2017.
- [77] O. A. Howlett, N. A. Lannin, L. Ada, and C. McKinstry, "Functional electrical stimulation improves activity after stroke: a systematic review with meta-analysis," *Arch Phys Med Rehabil*, vol. 96, no. 5, pp. 934-43, May, 2015.
- [78] C. Stein, C. G. Fritsch, C. Robinson, G. Sbruzzi, and R. D. M. Plentz, "Effects of electrical stimulation in spastic muscles after stroke: Systematic review and meta-analysis of randomized controlled trials," *Stroke*, July 14, 2015, 2015.

- [79] J. Eraifej, W. Clark, B. France, S. Desando, and D. Moore, "Effectiveness of upper limb functional electrical stimulation after stroke for the improvement of activities of daily living and motor function: a systematic review and meta-analysis," *Systematic Reviews*, vol. 6, no. 1, pp. 40, 2017/02/28, 2017.
- [80] G. E. Mann, J. H. Burridge, L. J. Malone, and P. W. Strike, "A pilot study to investigate the effects of electrical stimulation on recovery of hand function and sensation in subacute stroke patients," *Neuromodulation*, vol. 8, no. 3, pp. 193-202, Jul, 2005.
- [81] N. Yozbatiran, L. Der-Yeghiaian, and S. C. Cramer, "A standardized approach to performing the Action Research Arm Test," *Neurorehabil Neural Repair*, vol. 22, no. 1, pp. 78-90, Jan-Feb, 2008.
- [82] R. A. Bos, C. J. W. Haarman, T. Stortelder, K. Nizamis, J. L. Herder, A. H. A. Stienen, and D. H. Plettenburg, "A structured overview of trends and technologies used in dynamic hand orthoses," *Journal of NeuroEngineering and Rehabilitation*, vol. 13, pp. 62, 2016.
- [83] H. I. Krebs, N. Hogan, M. L. Aisen, and B. T. Volpe, "Robot-aided neurorehabilitation," *IEEE Transactions on Rehabilitation Engineering*, vol. 6, no. 1, pp. 75-87, 1998.
- [84] A. A. Frolov, O. Mokienko, R. Lyukmanov, E. Biryukova, S. Kotov, L. Turbina, G. Nadareyshvily, and Y. Bushkova, "Post-stroke rehabilitation training with a motor-imagery-based Brain-Computer Interface (BCI)-controlled hand exoskeleton: A randomized controlled multicenter trial," *Front Neurosci*, vol. 11, pp. 400, 2017.
- [85] M. Hallett, "Review: Plasticity in the human motor system," *The Neuroscientist*, vol. 5, no. 5, pp. 324-332, 1999/09/01, 1999.
- [86] D. O. Hebb, *The organization of behavior; A neuropsychological theory*, New York: John Wiley and Sons, 1949.
- [87] J. Mehrholz, M. Pohl, T. Platz, J. Kugler, and B. Elsner, "Electromechanical and robot-assisted arm training for improving activities of daily living, arm function, and arm muscle strength after stroke," *Cochrane Database Syst Rev*, vol. 9, pp. Cd006876, Sep 3, 2018.
- [88] H. Rodgers, L. Shaw, H. Bosomworth, L. Aird, N. Alvarado, S. Andole, D. L. Cohen, J. Dawson, J. Eyre, T. Finch, G. A. Ford, J. Hislop, S. Hogg, D. Howel, N. Hughes, H. I. Krebs, C. Price, L. Rochester, E. Stamp, L. Ternent, D. Turner, L. Vale, E. Warburton, F. van Wijck, and S. Wilkes, "Robot Assisted Training for the Upper Limb after Stroke (RATULS): study protocol for a randomised controlled trial," *Trials*, vol. 18, no. 1, pp. 340, 2017/07/20, 2017.
- [89] J. Laut, M. Porfiri, and P. Raghavan, "The present and future of robotic technology in rehabilitation," *Current physical medicine and rehabilitation reports*, vol. 4, no. 4, pp. 312-319, 11/19, 2016.
- [90] C. J. Shatz, "The Developing Brain," *Scientific American*, no. 267, pp. 60-67, 1992.
- [91] N. Caporale, and Y. Dan, "Spike timing-dependent plasticity: A Hebbian learning rule," *Annual Review of Neuroscience*, vol. 31, no. 1, pp. 25-46, 2008/07/01, 2008.
- [92] J. B. Carmel, H. Kimura, and J. H. Martin, "Electrical stimulation of motor cortex in the uninjured hemisphere after chronic unilateral injury promotes recovery of skilled locomotion through ipsilateral control," *J Neurosci*, vol. 34, no. 2, pp. 462-6, Jan 08, 2014.
- [93] W. Song, A. Amer, D. Ryan, and J. H. Martin, "Combined motor cortex and spinal cord neuromodulation promotes corticospinal system functional and structural plasticity and motor function after injury," *Exp Neurol*, vol. 277, pp. 46-57, Mar, 2016.
- [94] K. Stefan, E. Kunesch, L. G. Cohen, R. Benecke, and J. Classen, "Induction of plasticity in the human motor cortex by paired associative stimulation," *Brain*, vol. 123 Pt 3, pp. 572-84, Mar, 2000.
- [95] A. Jackson, J. Mavoori, and E. E. Fetz, "Long-term motor cortex plasticity induced by an electronic neural implant," *Nature*, vol. 444, pp. 56, 10/22/online, 2006.
- [96] Y. Nishimura, S. I. Perlmutter, R. W. Eaton, and E. E. Fetz, "Spike-timing-dependent plasticity in primate corticospinal connections induced during free behavior," *Neuron*, vol. 80, no. 5, pp. 1301-9, Dec 4, 2013.

- [97] A. Biasiucci, R. Leeb, I. Iturrate, S. Perdakis, A. Al-Khodairy, T. Corbet, A. Schnider, T. Schmidlin, H. Zhang, M. Bassolino, D. Viceic, P. Vuadens, A. G. Guggisberg, and J. d. R. Millán, "Brain-actuated functional electrical stimulation elicits lasting arm motor recovery after stroke," *Nature Communications*, vol. 9, no. 1, pp. 2421, 2018/06/20, 2018.
- [98] D. A. Bolton, J. H. Cauraugh, and H. A. Hausenblas, "Electromyogram-triggered neuromuscular stimulation and stroke motor recovery of arm/hand functions: a meta-analysis," *J Neurol Sci*, vol. 223, no. 2, pp. 121-7, Aug 30, 2004.
- [99] S. J. Groiss, L. Wojtecki, M. Südmeyer, and A. Schnitzler, "Deep brain stimulation in Parkinson's Disease," *Therapeutic Advances in Neurological Disorders*, vol. 2, no. 6, pp. 20-28, 2009.
- [100] R. M. Gorodnichev, E. A. Pivovarova, A. Pukhov, S. A. Moiseev, A. A. Savokhin, T. R. Moshonkina, N. A. Shcherbakova, V. A. Kilimnik, V. A. Selionov, I. B. Kozlovskaja, V. R. Edgerton, and Y. P. Gerasimenko, "[Transcutaneous electrical stimulation of the spinal cord: non-invasive tool for activation of locomotor circuitry in human] (Article in Russian)," *Fiziol Cheloveka*, vol. 38, no. 2, pp. 46-56, Mar-Apr, 2012.
- [101] K. Minassian, I. Persy, F. Rattay, M. R. Dimitrijevic, C. Hofer, and H. Kern, "Posterior root-muscle reflexes elicited by transcutaneous stimulation of the human lumbosacral cord," *Muscle & Nerve*, vol. 35, no. 3, pp. 327-336, 2007.
- [102] S. Musallam, B. D. Corneil, B. Greger, H. Scherberger, and R. A. Andersen, "Cognitive control signals for neural prosthetics," *Science*, vol. 305, no. 5681, pp. 258, 2004.
- [103] C. E. Bouton, A. Shaikhouni, N. V. Annetta, M. A. Bockbrader, D. A. Friedenberg, D. M. Nielson, G. Sharma, P. B. Sederberg, B. C. Glenn, W. J. Mysiw, A. G. Morgan, M. Deogaonkar, and A. R. Rezai, "Restoring cortical control of functional movement in a human with quadriplegia," *Nature*, vol. 533, no. 7602, pp. 247-50, May 12, 2016.
- [104] T. Aflalo, S. Kellis, C. Klaes, B. Lee, Y. Shi, K. Pejsa, K. Shanfield, S. Hayes-Jackson, M. Aisen, C. Heck, C. Liu, and R. A. Andersen, "Decoding motor imagery from the posterior parietal cortex of a tetraplegic human," *Science*, vol. 348, no. 6237, pp. 906, 2015.
- [105] N. Mrachacz-Kersting, S. R. Kristensen, I. K. Niazi, and D. Farina, "Precise temporal association between cortical potentials evoked by motor imagination and afference induces cortical plasticity," *J Physiol*, vol. 590, no. 7, pp. 1669-82, Apr 01, 2012.
- [106] R. Thorsen, D. Dalla Costa, S. Chiaramonte, L. Binda, E. Beghi, T. Redaelli, E. Occhi, and M. Ferrarin, "A noninvasive neuroprosthesis augments hand grasp force in individuals with cervical spinal cord injury: The functional and therapeutic effects," *The Scientific World Journal*, vol. 2013, pp. 7, 2013.
- [107] M. Rakos, A. Hahn, E. Uher, and M. Edenhofer, "EMG triggered rehabilitation of complex movements—biofeedback/stimulation system STIWELL med4."
- [108] National Institute for Health and Clinical Excellence (NICE), "Functional electrical stimulation for drop foot of central neurological origin," *NICE Guidance*, vol. IPG278, 2009.
- [109] M. D. Štrbac, N. M. Malešević, R. Čobeljić, and L. Schwirtlich, "Feedback control of the forearm movement of tetraplegic patient based on Microsoft Kinect and multi-pad electrodes," *Journal of Automatic Control*, vol. 21, pp. 7-11, 2013.
- [110] M. Jeannerod, "Intersegmental coordination during reaching at natural visual objects," *Attention and Performance*, pp. 153-168, 1981, 1981.
- [111] R. C. Lyle, "A performance test for assessment of upper limb function in physical rehabilitation treatment and research," *Int J Rehabil Res*, vol. 4, no. 4, pp. 483-92, 1981.
- [112] C. J. Shatz, "The developing brain," *Scientific American*, vol. 267, no. 3, pp. 60-67, 1992.
- [113] J. L. Taylor, and P. G. Martin, "Voluntary motor output is altered by spike-timing-dependent changes in the human corticospinal pathway," *J Neurosci*, vol. 29, no. 37, pp. 11708-16, Sep 16, 2009.

- [114] K. L. Bunday, and M. A. Perez, "Motor recovery after spinal cord injury enhanced by strengthening corticospinal synaptic transmission," *Curr Biol*, vol. 22, no. 24, pp. 2355-61, Dec 18, 2012.
- [115] D. G. Everaert, A. K. Thompson, S. L. Chong, and R. B. Stein, "Does functional electrical stimulation for foot drop strengthen corticospinal connections?," *Neurorehabil Neural Repair*, vol. 24, no. 2, pp. 168-77, Feb, 2010.
- [116] M. B. Popovic, D. B. Popovic, T. Sinkjaer, A. Stefanovic, and L. Schwirtlich, "Clinical evaluation of functional electrical therapy in acute hemiplegic subjects," *J Rehabil Res Dev*, vol. 40, no. 5, pp. 443-53, Sep-Oct, 2003.
- [117] C. Freeman, T. Exell, K. Meadmore, E. Hallewell, and A. M. Hughes, "Computational models of upper-limb motion during functional reaching tasks for application in FES-based stroke rehabilitation," *Biomed Tech (Berl)*, vol. 60, no. 3, pp. 179-91, Jun, 2015.
- [118] J. H. van der Lee, H. Beckerman, G. J. Lankhorst, and L. M. Bouter, "The responsiveness of the Action Research Arm test and the Fugl-Meyer Assessment scale in chronic stroke patients," *J Rehabil Med*, vol. 33, no. 3, pp. 110-3, Mar, 2001.
- [119] T. Platz, C. Pinkowski, F. van Wijck, I. H. Kim, P. di Bella, and G. Johnson, "Reliability and validity of arm function assessment with standardized guidelines for the Fugl-Meyer Test, Action Research Arm Test and Box and Block Test: a multicentre study," *Clin Rehabil*, vol. 19, no. 4, pp. 404-11, Jun, 2005.
- [120] J. H. Van der Lee, V. De Groot, H. Beckerman, R. C. Wagenaar, G. J. Lankhorst, and L. M. Bouter, "The intra- and interrater reliability of the action research arm test: a practical test of upper extremity function in patients with stroke," *Arch Phys Med Rehabil*, vol. 82, no. 1, pp. 14-9, Jan, 2001.
- [121] P. Taylor, "Electrical stimulation of the upper limb.," http://www.odstockmedical.com/sites/default/files/1_uper_limb_tips_and_tricks_userday_2017.pdf, Odstock Medical Ltd, ed., 2017.
- [122] C. Fekete, I. Eriks-Hoogland, M. Baumberger, A. Catz, M. Itzkovich, H. Luthi, M. W. Post, E. von Elm, A. Wyss, and M. W. Brinkhof, "Development and validation of a self-report version of the Spinal Cord Independence Measure (SCIM III)," *Spinal Cord*, vol. 51, no. 1, pp. 40-7, Jan, 2013.
- [123] M. L. McHugh, "Interrater reliability: the kappa statistic," *Biochemia Medica*, vol. 22, no. 3, pp. 276-282, 2012.
- [124] C. Ethier, J. A. Gallego, and L. E. Miller, "Brain-controlled neuromuscular stimulation to drive neural plasticity and functional recovery," *Curr Opin Neurobiol*, vol. 33, pp. 95-102, Aug, 2015.
- [125] S. Li, and G. E. Francisco, "New insights into the pathophysiology of post-stroke spasticity," *Front Hum Neurosci*, vol. 9, pp. 192, 2015.
- [126] A. R. Fugl-Meyer, L. Jääskö, I. Leyman, S. Olsson, and S. Steglind, "The post-stroke hemiplegic patient. 1. a method for evaluation of physical performance," *Scandinavian journal of rehabilitation medicine*, vol. 7, no. 1, pp. 13-31, 1975.
- [127] D. J. Gladstone, C. J. Danells, and S. E. Black, "The Fugl-Meyer assessment of motor recovery after stroke: a critical review of its measurement properties," *Neurorehabil Neural Repair*, vol. 16, no. 3, pp. 232-40, Sep, 2002.
- [128] S. Ashford, M. Slade, and L. Turner-Stokes, "Conceptualisation and development of the arm activity measure (ArMA) for assessment of activity in the hemiparetic arm," *Disabil Rehabil*, vol. 35, no. 18, pp. 1513-8, Aug, 2013.
- [129] S. J. Page, G. D. Fulk, and P. Boyne, "Clinically important differences for the upper-extremity Fugl-Meyer Scale in people with minimal to moderate impairment due to chronic stroke," *Phys Ther*, vol. 92, no. 6, pp. 791-8, Jun, 2012.
- [130] V. Mathiowetz, G. Volland, N. Kashman, and K. Weber, "Adult norms for the Box and Block Test of manual dexterity," *Am J Occup Ther*, vol. 39, no. 6, pp. 386-91, Jun, 1985.

- [131] A. D. Pandyan, G. R. Johnson, C. I. Price, R. H. Curless, M. P. Barnes, and H. Rodgers, "A review of the properties and limitations of the Ashworth and modified Ashworth Scales as measures of spasticity," *Clin Rehabil*, vol. 13, no. 5, pp. 373-83, Oct, 1999.
- [132] N. Y. Harel, and J. B. Carmel, "Paired stimulation to promote lasting augmentation of corticospinal circuits," *Neural Plasticity*, vol. 2016, pp. 11, 2016.
- [133] K. Stefan, E. Kunesch, R. Benecke, L. G. Cohen, and J. Classen, "Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation," *The Journal of Physiology*, vol. 543, no. Pt 2, pp. 699-708, 2002.
- [134] N. Mrachacz-Kersting, and N. Jiang, "Efficient neuroplasticity induction in chronic stroke patients by an associative brain-computer interface," vol. 115, no. 3, pp. 1410-21, Mar, 2016.
- [135] G. I. Barsi, D. B. Popovic, I. M. Tarkka, T. Sinkjaer, and M. J. Grey, "Cortical excitability changes following grasping exercise augmented with electrical stimulation," *Exp Brain Res*, vol. 191, no. 1, pp. 57-66, Oct, 2008.
- [136] T. Yamaguchi, K. Sugawara, S. Tanaka, N. Yoshida, K. Saito, S. Tanabe, Y. Muraoka, and M. Liu, "Real-time changes in corticospinal excitability during voluntary contraction with concurrent electrical stimulation," *PLOS ONE*, vol. 7, no. 9, pp. e46122, 2012.
- [137] A. M. Mishra, A. Pal, D. Gupta, and J. B. Carmel, "Paired motor cortex and cervical epidural electrical stimulation timed to converge in the spinal cord promotes lasting increases in motor responses," *The Journal of Physiology*, vol. 595, no. 22, pp. 6953-6968, 2017, 2017.
- [138] V. Di Lazzaro, and J. C. Rothwell, "Corticospinal activity evoked and modulated by non-invasive stimulation of the intact human motor cortex," *J Physiol*, vol. 592, no. 19, pp. 4115-28, Oct 1, 2014.
- [139] S. R. Jaiser, J. D. Barnes, S. N. Baker, and M. R. Baker, "A multiple regression model of normal central and peripheral motor conduction times," *Muscle Nerve*, vol. 51, no. 5, pp. 706-12, May, 2015.
- [140] J. L. Taylor, G. M. Allen, J. E. Butler, and S. C. Gandevia, "Effect of contraction strength on responses in biceps brachii and adductor pollicis to transcranial magnetic stimulation," *Exp Brain Res*, vol. 117, no. 3, pp. 472-8, Dec, 1997.
- [141] Minitab.com, *Minitab Assistant White Paper: 1-Sample t-Test*, Minitab, http://support.minitab.com/en-us/minitab/17/Assistant_One_Sample_t.pdf, 2017.
- [142] Minitab.com, *Minitab Assistant White Paper: 2-Sample t-Test*, Minitab, http://support.minitab.com/en-us/minitab/17/Assistant_Two_Sample_t.pdf, 2017.
- [143] A. Samii, E. M. Wassermann, and M. Hallett, "Post-exercise depression of motor evoked potentials as a function of exercise duration," *Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control*, vol. 105, no. 5, pp. 352-356, 1997/10/01/, 1997.
- [144] J. P. Brasil-Neto, A. Pascual-Leone, J. Valls-Sole, A. Cammarota, L. G. Cohen, and M. Hallett, "Postexercise depression of motor evoked potentials: a measure of central nervous system fatigue," *Exp Brain Res*, vol. 93, no. 1, pp. 181-4, 1993.
- [145] S. C. Gandevia, "Spinal and supraspinal factors in human muscle fatigue," *Physiol Rev*, vol. 81, no. 4, pp. 1725-89, Oct, 2001.
- [146] A. Kido Thompson, and R. B. Stein, "Short-term effects of functional electrical stimulation on motor-evoked potentials in ankle flexor and extensor muscles," *Exp Brain Res*, vol. 159, no. 4, pp. 491-500, Dec, 2004.
- [147] S. Kotan, S. Kojima, S. Miyaguchi, K. Sugawara, and H. Onishi, "Depression of corticomotor excitability after muscle fatigue induced by electrical stimulation and voluntary contraction," *Front Hum Neurosci*, vol. 9, pp. 363, 2015.
- [148] A. Wolters, F. Sandbrink, A. Schlottmann, E. Kunesch, K. Stefan, L. G. Cohen, R. Benecke, and J. Classen, "A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex," *J Neurophysiol*, vol. 89, no. 5, pp. 2339-45, May, 2003.

- [149] R. G. Carson, and N. C. Kennedy, "Modulation of human corticospinal excitability by paired associative stimulation," *Front Hum Neurosci*, vol. 7, pp. 823, Dec 3, 2013.
- [150] M. C. Ridding, and J. L. Taylor, "Mechanisms of motor-evoked potential facilitation following prolonged dual peripheral and central stimulation in humans," *J Physiol*, vol. 537, no. Pt 2, pp. 623-31, Dec 1, 2001.
- [151] K. M. Foyosal, F. de Carvalho, and S. N. Baker, "Spike timing-dependent plasticity in the long-latency stretch reflex following paired stimulation from a wearable electronic device," *J Neurosci*, vol. 36, no. 42, pp. 10823-10830, Oct 19, 2016.
- [152] S. M. Schabrun, M. C. Ridding, M. P. Galea, P. W. Hodges, and L. S. Chipchase, "Primary sensory and motor cortex excitability are co-modulated in response to peripheral electrical nerve stimulation," *PLoS One*, vol. 7, no. 12, pp. e51298, 2012.
- [153] R. Foyosal, "Motor system plasticity induced by non-invasive stimuli," Doctor of Medicine (Thesis), Institute of Neuroscience, Newcastle University, 2018.
- [154] S. B. Godfrey, P. S. Lum, E. Chan, and M. L. Harris-Love, "Cortical effects of repetitive finger flexion- vs. extension-resisted tracking movements: a TMS study," *Journal of Neurophysiology*, vol. 109, no. 4, pp. 1009-1016, 2013/02/15, 2012.
- [155] M. Tinazzi, S. Zarattini, M. Valeriani, S. Romito, S. Farina, G. Moretto, N. Smania, A. Fiaschi, and G. Abbruzzese, "Long-lasting modulation of human motor cortex following prolonged transcutaneous electrical nerve stimulation (TENS) of forearm muscles: evidence of reciprocal inhibition and facilitation," *Exp Brain Res*, vol. 161, no. 4, pp. 457-64, Mar, 2005.
- [156] A. Lackmy-Vallee, W. Klomjai, B. Bussel, R. Katz, and N. Roche, "Anodal transcranial direct current stimulation of the motor cortex induces opposite modulation of reciprocal inhibition in wrist extensor and flexor," *J Neurophysiol*, vol. 112, no. 6, pp. 1505-15, Sep 15, 2014.
- [157] P. G. Martin, J. L. Smith, J. E. Butler, S. C. Gandevia, and J. L. Taylor, "Fatigue-sensitive afferents inhibit extensor but not flexor motoneurons in humans," *The Journal of Neuroscience*, vol. 26, no. 18, pp. 4796, 2006.
- [158] B. Zaaimi, S. A. Edgley, D. S. Soteropoulos, and S. N. Baker, "Changes in descending motor pathway connectivity after corticospinal tract lesion in macaque monkey," *Brain*, vol. 135, no. Pt 7, pp. 2277-89, Jul, 2012.
- [159] U. Windhorst, "Muscle proprioceptive feedback and spinal networks," *Brain Res Bull*, vol. 73, no. 4-6, pp. 155-202, Jul 12, 2007.
- [160] S.-H. Chang, G. E. Francisco, and S. Li, "Botulinum toxin injection improved voluntary motor control in selected patients with post-stroke spasticity," *Neural Regeneration Research*, vol. 7, no. 18, pp. 1436-1439, 2012.
- [161] J. Levy, F. Molteni, G. Cannaviello, T. Lansaman, N. Roche, and D. Bensmail, "Does botulinum toxin treatment improve upper limb active function?," *Ann Phys Rehabil Med*, Jun 27, 2018.
- [162] A. Mukherjee, and A. Chakravarty, "Spasticity mechanisms – for the clinician," *Frontiers in Neurology*, vol. 1, pp. 149, 2010.
- [163] S. Li, "Spasticity, motor recovery, and neural plasticity after stroke," *Frontiers in Neurology*, vol. 8, pp. 120, 2017.
- [164] E. Cakar, G. Akyuz, O. Durmus, L. Bayman, I. Yagci, E. Karadag-Saygi, and O. H. Gunduz, "The relationships of motor-evoked potentials to hand dexterity, motor function, and spasticity in chronic stroke patients: a transcranial magnetic stimulation study," *Acta Neurologica Belgica*, vol. 116, no. 4, pp. 481-487, 2016/12/01, 2016.
- [165] Z. A. Wright, W. Z. Rymer, and M. W. Slutzky, "Reducing abnormal muscle coactivation after stroke using a myoelectric-computer interface: A pilot study," *Neurorehabil Neural Repair*, vol. 28, no. 5, pp. 443-51, Jun, 2014.
- [166] M. A. Perez, B. K. Lungholt, K. Nyborg, and J. B. Nielsen, "Motor skill training induces changes in the excitability of the leg cortical area in healthy humans," *Exp Brain Res*, vol. 159, no. 2, pp. 197-205, Nov, 2004.

- [167] D. G. Sayenko, D. A. Atkinson, C. J. Dy, K. M. Gurley, V. L. Smith, C. Angeli, S. J. Harkema, V. R. Edgerton, and Y. P. Gerasimenko, "Spinal segment-specific transcutaneous stimulation differentially shapes activation pattern among motor pools in humans," *J Appl Physiol* (1985), vol. 118, no. 11, pp. 1364-74, Jun 1, 2015.
- [168] A. Maertens de Noordhout, J. C. Rothwell, P. D. Thompson, B. L. Day, and C. D. Marsden, "Percutaneous electrical stimulation of lumbosacral roots in man," *J Neurol Neurosurg Psychiatry*, vol. 51, no. 2, pp. 174-81, Feb, 1988.
- [169] A. R. Ward, and V. J. Robertson, "Sensory, motor, and pain thresholds for stimulation with medium frequency alternating current," *Arch Phys Med Rehabil*, vol. 79, no. 3, pp. 273-8, Mar, 1998.
- [170] Y. H. Jeon, "Spinal cord stimulation in pain management: A review," *Korean J Pain*, vol. 25, no. 3, pp. 143-150, 7/, 2012.
- [171] J. Jiao, W. Jensen, K. R. Harreby, and C. Sevcencu, "The effect of spinal cord stimulation on epileptic seizures," *Neuromodulation*, vol. 19, no. 2, pp. 154-60, Feb, 2016.
- [172] O. Samotus, A. Parrent, and M. Jog, "Spinal cord stimulation therapy for gait dysfunction in advanced Parkinson's Disease patients," *Mov Disord*, vol. 33, no. 5, pp. 783-792, May, 2018.
- [173] E. Rejc, C. Angeli, and S. Harkema, "Effects of lumbosacral spinal cord epidural stimulation for standing after chronic complete paralysis in humans," *PLoS One*, vol. 10, no. 7, pp. e0133998, 2015.
- [174] A. M. Mishra, A. Pal, D. Gupta, and J. B. Carmel, "Paired motor cortex and cervical epidural electrical stimulation timed to converge in the spinal cord promotes lasting increases in motor responses," *J Physiol*, vol. 595, no. 22, pp. 6953-6968, 15 November 2017, 2017.
- [175] A. R. Ward, and W. L. Chuen, "Lowering of sensory, motor, and pain-tolerance thresholds with burst duration using kilohertz-frequency alternating current electric stimulation: part II," *Arch Phys Med Rehabil*, vol. 90, no. 9, pp. 1619-27, Sep, 2009.
- [176] R. M. Palmieri, C. D. Ingersoll, and M. A. Hoffman, "The Hoffmann reflex: Methodologic considerations and applications for use in sports medicine and athletic training research," *Journal of Athletic Training*, vol. 39, no. 3, pp. 268-277, Jul-Sep, 2004.
- [177] R. D. Herbert, and S. C. Gandevia, "Twitch interpolation in human muscles: mechanisms and implications for measurement of voluntary activation," *J Neurophysiol*, vol. 82, no. 5, pp. 2271-83, Nov, 1999.
- [178] J. Kopec, J. Delbeke, and A. J. McComas, "Refractory period studies in a human neuromuscular preparation," *J Neurol Neurosurg Psychiatry*, vol. 41, no. 1, pp. 54-64, Jan, 1978.
- [179] J. H. McAuley, and C. D. Marsden, "Physiological and pathological tremors and rhythmic central motor control," *Brain*, vol. 123, no. 8, pp. 1545-1567, 2000.
- [180] R. J. Elble, and J. E. Randall, "Motor-unit activity responsible for 8- to 12-Hz component of human physiological finger tremor," *J Neurophysiol*, vol. 39, no. 2, pp. 370-83, Mar, 1976.
- [181] L. P. Kudina, and R. E. Andreeva, "Triplet firing origin in human motor units: emerging hypotheses," *Experimental Brain Research*, vol. 234, no. 3, pp. 837-844, 2016/03/01, 2016.
- [182] A. N. Sharpe, and A. Jackson, "Upper-limb muscle responses to epidural, subdural and intraspinal stimulation of the cervical spinal cord," *J Neural Eng*, vol. 11, no. 1, pp. 016005, Feb, 2014.
- [183] A. Jackson, "10Hz Oscillations in MEPs following epidural SCS ", Personal Communication, 2018.
- [184] A. Takeoka, I. Vollenweider, G. Courtine, and S. Arber, "Muscle spindle feedback directs locomotor recovery and circuit reorganization after spinal cord injury," *Cell*, vol. 159, no. 7, pp. 1626-39, Dec 18, 2014.
- [185] A. Tedeschi, and F. Bradke, "A New "Spin" on Recovery after Spinal Cord Injury," *Cell*, vol. 159, no. 7, pp. 1494-1496, 2014.

- [186] M. Lidiérth, and P. D. Wall, "Synchronous inherent oscillations of potentials within the rat lumbar spinal cord," *Neurosci Lett*, vol. 220, no. 1, pp. 25-8, Dec 6, 1996.
- [187] Y. Ootsuka, T. Xu, and N. Terui, "The spinally mediated 10-Hz rhythm in the sympathetic nerve activity of cats," *Journal of the Autonomic Nervous System*, vol. 54, no. 2, pp. 89-103, 1995/08/04/, 1995.
- [188] J. A. Norton, D. E. Wood, J. F. Marsden, and B. L. Day, "Spinally generated electromyographic oscillations and spasms in a low-thoracic complete paraplegic," *Mov Disord*, vol. 18, no. 1, pp. 101-6, Jan, 2003.
- [189] A. A. Stefane, N. B. Stuart, G. Katie, B. Jorge, and T. Christine, "Spasms after spinal cord injury show low-frequency intermuscular coherence," *Journal of Neurophysiology*, vol. 120, no. 4, pp. 1765-1771.
- [190] J. A. Beres-Jones, T. D. Johnson, and S. J. Harkema, "Clonus after human spinal cord injury cannot be attributed solely to recurrent muscle-tendon stretch," *Exp Brain Res*, vol. 149, no. 2, pp. 222-36, Mar, 2003.
- [191] R. Iansek, "The effects of reflex path length on clonus frequency in spastic muscles," *J Neurol Neurosurg Psychiatry*, vol. 47, no. 10, pp. 1122-4, Oct, 1984.
- [192] C. N. Christakos, N. A. Papadimitriou, and S. Erimaki, "Parallel neuronal mechanisms underlying physiological force tremor in steady muscle contractions of humans," *J Neurophysiol*, vol. 95, no. 1, pp. 53-66, Jan, 2006.
- [193] M. R. Dimitrijevic, M. M. Dimitrijevic, A. M. Sherwood, and J. Faganel, "Neurophysiological evaluation of chronic spinal cord stimulation in patients with upper motor neuron disorders," *International Rehabilitation Medicine*, vol. 2, no. 2, pp. 82-85, 1980.
- [194] M. M. Pinter, F. Gerstenbrand, and M. R. Dimitrijevic, "Epidural electrical stimulation of posterior structures of the human lumbosacral cord: 3. Control Of spasticity," *Spinal Cord*, vol. 38, no. 9, pp. 524-31, Sep, 2000.
- [195] J. M. Gracies, S. Meunier, E. Pierrot-Deseilligny, and M. Simonetta, "Pattern of propriospinal-like excitation to different species of human upper limb motoneurons," *The Journal of Physiology*, vol. 434, pp. 151-167, 1991.
- [196] S. N. Baker, "Oscillatory interactions between sensorimotor cortex and the periphery," *Curr Opin Neurobiol*, vol. 17, no. 6, pp. 649-55, Dec, 2007.
- [197] E. R. Williams, D. S. Soteropoulos, and S. N. Baker, "Spinal interneuron circuits reduce approximately 10-Hz movement discontinuities by phase cancellation," *Proc Natl Acad Sci U S A*, vol. 107, no. 24, pp. 11098-103, Jun 15, 2010.
- [198] E. R. Williams, and S. N. Baker, "Renshaw cell recurrent inhibition improves physiological tremor by reducing corticomuscular coupling at 10 Hz," *The Journal of Neuroscience*, vol. 29, no. 20, pp. 6616, 2009.
- [199] R. Mazzocchio, and A. Rossi, "Role of Renshaw cells in amyotrophic lateral sclerosis," *Muscle Nerve*, vol. 41, no. 4, pp. 441-3, Apr, 2010.
- [200] M. Piotrkiewicz, and D. Młóżniak, "Are human digit muscles devoid of recurrent inhibition?," *Frontiers in Cellular Neuroscience*, vol. 9, no. 507, 2016-January-11, 2016.
- [201] E. Bravo-Esteban, J. Taylor, M. Alexandre, C. Simon-Martinez, D. Torricelli, J. L. Pons, G. Avila-Martin, I. Galan-Arriero, and J. Gomez-Soriano, "Longitudinal estimation of intramuscular Tibialis Anterior coherence during subacute spinal cord injury: relationship with neurophysiological, functional and clinical outcome measures," *J Neuroeng Rehabil*, vol. 14, no. 1, pp. 58, Jun 15, 2017.
- [202] S. Heinrich, K. Rapp, U. Rissmann, C. Becker, and H. H. König, "Cost of falls in old age: a systematic review," *Osteoporos Int*, vol. 21, no. 6, pp. 891-902, Jun, 2010.
- [203] P. Craig, P. Dieppe, S. Macintyre, S. Michie, I. Nazareth, and M. Petticrew, "Developing and evaluating complex interventions: new guidance," Medical Research Council, 2006.
- [204] M. S. Kleinman, and J. W. Mold, "Defining the Components of the Research Pipeline," *Clinical and Translational Science*, vol. 2, no. 4, pp. 312-314, 07/15, 2009.

- [205] B. Cheeran, L. Cohen, B. Dobkin, G. Ford, R. Greenwood, D. Howard, M. Husain, M. Macleod, R. Nudo, J. Rothwell, A. Rudd, J. Teo, N. Ward, and S. Wolf, "The future of restorative neurosciences in stroke: driving the translational research pipeline from basic science to rehabilitation of people after stroke," *Neurorehabil Neural Repair*, vol. 23, no. 2, pp. 97-107, Feb, 2009.
- [206] J. Bernhardt, K. Borschmann, L. Boyd, S. T. Carmichael, D. Corbett, S. C. Cramer, T. Hoffmann, G. Kwakkel, S. Savitz, G. Saposnik, M. Walker, and N. Ward, "Moving Rehabilitation Research Forward: Developing Consensus Statements for Rehabilitation and Recovery Research," *Neurorehabil Neural Repair*, vol. 31, no. 8, pp. 694-698, Aug, 2017.
- [207] N. Donaldson, "Killing the goose," *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine*, pp. 0954411917740168, 2017.
- [208] M. Tolikas, A. Antoniou, and D. E. Ingber, "The Wyss institute: A new model for medical technology innovation and translation across the academic-industrial interface," *Bioengineering & Translational Medicine*, vol. 2, no. 3, pp. 247-257, 2017/09/01, 2017.
- [209] Wings For Life. 01/10/2018; <https://www.wingsforlife.com/>.
- [210] Aspire: Supporting people with spinal injury. 01/10/2018; <https://www.aspire.org.uk/>.
- [211] Stroke Association. 01/10/2018; <https://www.stroke.org.uk/>.
- [212] Wellcome Trust. 01/10/2018; <https://wellcome.ac.uk/>.
- [213] R. Merletti, R. Acimovic, S. Grobelnik, and G. Cvilak, "Electrophysiological orthosis for the upper extremity in hemiplegia: feasibility study," *Arch Phys Med Rehabil*, vol. 56, no. 12, pp. 507-13, Dec, 1975.
- [214] A. Cuesta-Gómez, F. Molina-Rueda, M. Carratala-Tejada, E. Imatz-Ojanguren, D. Torricelli, and J. C. Miangolarra-Page, "The use of functional electrical stimulation on the upper Limb and interscapular muscles of patients with stroke for the improvement of reaching movements: A feasibility study," *Frontiers in Neurology*, vol. 8, pp. 186, 2017.
- [215] C. T. Moritz, "Now is the critical time for engineered neuroplasticity," *Neurotherapeutics*, Jun 11, 2018.
- [216] G. Mann, P. Taylor, and R. Lane, "Accelerometer-triggered electrical stimulation for reach and grasp in chronic stroke patients: a pilot study," *Neurorehabil Neural Repair*, vol. 25, no. 8, pp. 774-80, Oct, 2011.
- [217] P. Taylor, G. Mann, J. Esnouf, H. Luckie, K. Warring, C. McFadden, C. Smith, and L. Kenney, "A randomised controlled trial of an accelerometer triggered functional electrical stimulation device for recovery of upper limb function in chronic stroke – The REACH project," *International Journal of Stroke*, vol. 9, no. S4, pp. 15-17, 2014.
- [218] P. M. Kluding, K. Dunning, M. W. O'Dell, S. S. Wu, J. Ginosian, J. Feld, and K. McBride, "Foot drop stimulation versus ankle foot orthosis after stroke: 30-week outcomes," *Stroke*, vol. 44, no. 6, pp. 1660-9, Jun, 2013.
- [219] S. Prenton, K. L. Hollands, and L. P. Kenney, "Functional electrical stimulation versus ankle foot orthoses for foot-drop: A meta-analysis of orthotic effects," *J Rehabil Med*, vol. 48, no. 8, pp. 646-656, Oct 5, 2016.
- [220] R. H. Da-Silva, F. van Wijck, L. Shaw, H. Rodgers, M. Balaam, L. Brkic, T. Ploetz, D. Jackson, K. Ladha, and C. I. Price, "Prompting arm activity after stroke: A clinical proof of concept study of wrist-worn accelerometers with a vibrating alert function," *Journal of Rehabilitation and Assistive Technologies Engineering*, vol. 5, pp. 2055668318761524, 2018/01/01, 2018.