The immediate effects of EMG-triggered neuromuscular electrical stimulation on cortical excitability and grip control in people with chronic stroke

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Health and Environmental Sciences

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Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Signed:

Juliet Rosie

30 June 2009

Acknowledgements

First I would like to thank my primary supervisor Denise Taylor; for support, direction and always seeing to the heart of things.

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To my family, friends and loved ones; thank you for looking out for me and after me through this long process, it could not have been done without you.

MEMORANDUM

Auckland University of Technology Ethics Committee (AUTEC)

To: Denise Taylor
From: **Madeline Banda** Executive Secretary, AUTEC
Date: 13 February 2008
Subject: Ethics Application Number 08/01 **The immediate changes in neural pathways and grip force control following an EMG-triggered electrical stimulation intervention in people with stroke.**

Dear Denise

Thank you for providing written evidence as requested. I am pleased to advise that it satisfies the points raised by the Auckland University of Technology Ethics Committee (AUTEC) at their meeting on 21 January 2008 and that I have approved your ethics application. This delegated approval is made in accordance with section 5.3.2.3 of AUTEC's *Applying for Ethics Approval: Guidelines and Procedures* and is subject to endorsement at AUTEC's meeting on 10 March 2008.

Your ethics application is approved for a period of three years until 13 February 2011.

I advise that as part of the ethics approval process, you are required to submit the following to AUTEC:

- A brief annual progress report using form EA2, which is available online through *http://www.aut.ac.nz/about/ethics*. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 13 February 2011;
- A brief report on the status of the project using form EA3, which is available online through *http://www.aut.ac.nz/about/ethics*. This report is to be submitted either when the approval expires on 13 February 2011 or on completion of the project, whichever comes sooner;

It is a condition of approval that AUTEC is notified of any adverse events or if the research does not commence. AUTEC approval needs to be sought for any alteration to the research, including any alteration of or addition to any documents that are provided to participants. You are reminded that, as applicant, you are responsible for ensuring that research undertaken under this approval occurs within the parameters outlined in the approved application.

Please note that AUTEC grants ethical approval only. If you require management approval from an institution or organisation for your research, then you will need to make the arrangements necessary to obtain this.

When communicating with us about this application, we ask that you use the application number and study title to enable us to provide you with prompt service. Should you have any further enquiries regarding this matter, you are welcome to contact Charles Grinter, Ethics Coordinator, by email at charles.grinter@aut.ac.nz or by telephone on 921 9999 at extension 8860.

On behalf of the AUTEC and myself, I wish you success with your research and look forward to reading about it in your reports.
Yours sincerely

Madeline Banda
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: Juliet Rosie, Gwyn Lewis

Abstract

Aim

The aim of this study was to identify the immediate effects on cortical excitability and grip control of a short intervention of EMG-triggered neuromuscular electrical stimulation, compared to voluntary activation of the finger flexor muscles, in people with chronic stroke.

Study Design

This experimental study used a within-subject design with experimental and control interventions.

Participants

Fifteen people with chronic stroke participated in the study.

Intervention

Participants performed a simple force tracking task with or without EMG-triggered neuromuscular electrical stimulation of the finger flexor muscles.

Main outcome measures

Cortical excitability was measured by single and paired-pulse transcranial magnetic stimulation. Multi-digit grip control accuracy was measured during ramp and sine wave force tracking tasks. Maximal grip strength was measured before and after each intervention to monitor muscle fatigue.

Results

No significant increases in cortico-motor excitability were found. Intracortical inhibition significantly increased following the EMG-triggered neuromuscular electrical stimulation intervention immediately post-intervention ($t = 2.466$, $p = .036$), and at 10 minutes post-intervention ($t = 2.45$, $p = .04$). Accuracy during one component of the

force tracking tasks significantly improved ($F(1, 14) = 4.701$, $p = .048$), following both EMG-triggered neuromuscular electrical stimulation and voluntary activation interventions. Maximal grip strength reduced significantly following both interventions, after the assessment of cortical excitability ($F(1, 8) = 9.197$, $p = .16$), and grip control ($F(1, 14) = 9.026$, $p = .009$).

Conclusions

EMG-triggered neuromuscular electrical stimulation during short duration force tracking training does not increase cortical excitability in participants with chronic stroke. Short duration force tracking training both with and without EMG-triggered neuromuscular electrical stimulation leads to improvements in training-specific aspects of grip control in people with chronic stroke.

1 Introduction

1.1 Outline of Study

The aim of this study was to identify the immediate effects on cortical excitability and grip control of a short period of electromyography (EMG)-triggered neuromuscular electrical stimulation (NMES) compared with voluntary activation of finger flexor muscles in a sample of people with stroke. Effects on cortico-motor and cortical excitability were measured by the use of single and paired-pulse transcranial magnetic stimulation (TMS); effects on grip control were measured using a multi-digit grip force tracking task. The current study is novel in investigating whether EMG-NMES will improve an objective measure of grip control following stroke. While previous studies have investigated the neural effects of EMG-NMES in healthy populations and following long term interventions in patient populations, the immediate effects on cortical excitability have not been investigated in participants with stroke.

1.2 Hypotheses

The following hypotheses were held:

1. Both EMG-NMES and the control protocol of voluntary activation unassisted by NMES will increase cortical excitability in people with stroke compared to baseline measures.
2. EMG-NMES will result in greater immediate increases in cortical excitability than the control protocol of voluntary activation unassisted by NMES.

3. Both EMG-NMES and the control protocol of voluntary activation unassisted by NMES will increase grip control ability in people with stroke compared to baseline measures.
4. EMG-NMES will result in greater immediate increases in grip control ability than the control protocol of voluntary activation unassisted by NMES.

1.3 Delimitations

The following delimitations apply to this study:

1. Grip control was measured using a force tracking task alone, and no functional outcome measures of grip control were taken.
2. Cortical excitability was measured using TMS. While presumptions about the excitability of cortical interneurons may be drawn from the paired pulse technique, the extent of spinal motoneuron excitability contribution to the results is not able to be identified with this technique.
3. The generalisability of results is limited to persons with a single unilateral stroke with some grip ability intact (able to pick up at least one block in the Box and Block Test).

1.4 Limitations

The following limitations apply to this study:

1. Grip control was assessed in participants' more affected hand only.
2. Aspects of equipment set up were determined by participant comfort and therefore not standardised.

1.5 Operational definitions

Grip control: the ability to produce, coordinate and adapt grip forces appropriate to load forces and task demands.

Grip force: forces acting perpendicular to the skin produced by the fingers and hand in contact with an object (Wheat, Salo, & Goodwin, 2004).

Load force: forces acting tangentially to the skin (Wheat et al., 2004) arising from the mechanical properties of an object (weight, surface friction, resistance to deformation) and/or produced during movement of an object (inertia, gravity, velocity) (Nowak & Hermsdörfer, 2005).

2 Literature Review

2.1 Introduction

To hold and lift an object efficiently and effectively a person must be able to predict its mechanical properties (weight, surface friction), make subtle adjustments to grip appropriate to those properties, and respond to changes in load from inertia, gravity or perturbations both anticipated and unexpected (Nowak & Hermsdörfer, 2005). Following stroke, strength, scaling of grip force, timing of grip force and selective finger movement are commonly impaired. These impairments contribute to reduced efficiency and effectiveness of grip. This chapter provides the theoretical foundations for the study by setting out an analysis of current literature directed at answering the following four core questions:

1. How do healthy adults control grip?
2. How does grip control change following a stroke?
3. Can we affect the neural pathways within the brain involved in grip control?
4. Can we improve grip control following stroke?

Hand aperture, proximal upper limb and trunk control are vital to effective grip (Sangole & Levin, 2007). This literature review is however limited in scope to the time point when the fingers interact with the object; the contact phase of grasp.

2.2 Grip control in healthy adults

2.2.1 Introduction.

Close synchrony between grip and load forces and efficient force production characterises grip control during upper limb lifting tasks in healthy adults. This control is enabled by feed-forward mechanisms, and supported by the structural arrangement and neurological control of hand musculature. Following an overview of the types of grip, each of these aspects of grip control in healthy adults will be addressed.

2.2.2 Types of grip.

There are three broad categories of grip; pinch, palmar and non-prehensile. Pinch grip involves prehension of the thumb to the tip, pad or lateral aspect (for example when turning a key in a lock) of another digit. In palmar grip the palm contacts the surface of the object; the fingers may be positioned cylindrically (for example holding a hammer or stair rail), or spherically (turning a jar lid or door knob). In non-prehensile grip the fingers do not oppose each other, such as when the fingers form a hook to carry a suitcase (Stanley & Tribuzie, 1992). Grip may be for power or precision or a combination of the two. Pinch grips are often used for precise handling. As more force can be exerted during palmar grip, palmar grips are used when power is required.

2.2.3 Feed-forward control of grip in healthy adults.

When an object is moved, grip force alters contemporaneously with changing load forces, with peaks in grip force occurring alongside or slightly prior to changes in load force that result from inertia, gravity and anticipated perturbations (Flanagan & Tresilian, 1994; Flanagan, Tresilian, & Wing, 1993; Flanagan & Wing, 1993, 1997).

Responses from receptors in the fingers and hand, nerve conduction velocity and muscle action speeds are too slow to explain the immediacy with which healthy adults are able to form, adjust and sustain grip appropriate to the properties of an object (Flanagan, Bowman, & Johansson, 2006; Flanagan, Vetter, Johansson, & Wolpert, 2003).

A healthy adult is able to adjust grip accurately for an object's perceived size, weight and surface friction before their fingers and hand make contact with it. It appears therefore that during grip we rely on motor commands that are generated by prediction of the properties of the object and the consequences of movement (Hermsdörfer, Elias, Cole, Quaney, & Nowak, 2008; Nowak, Glasauer, & Hermsdorfer, 2003, 2004). The hypothesis is that these motor commands are derived from an internal model, which draws together physical cues from visual and sensory information, and knowledge of the environment and body segments, in conjunction with the person's prior experiences. Accurate prediction of an object's properties will impact the amount of force used on contacting the object, in addition to altering hand aperture and proximal arm and trunk muscle activation and movement (Nowak, 2008). Grip and load forces remain closely coordinated even when the arm or person is moving (Flanagan & Tresilian, 1994; Flanagan et al., 1993; Flanagan & Wing, 1993). The close relationship between grip force and load force is maintained irrespective of the direction of forces on the load (Flanagan et al. 1993; Johansson et al. 1999; Kinoshita et al. 1997), the shape of the object (Goodwin, Jenmalm, & Johansson, 1998; Jenmalm, Dahlstedt, & Johansson, 2000) or the type of grip (Flanagan & Tresilian, 1994).

Grip control in healthy adults is very efficient, with forces used just above the minimum required to prevent the object slipping. This provides a safety margin to accommodate changes in load due to movement and unexpected perturbations (Nowak

& Hermsdörfer, 2003) while still allowing dexterous finger movement and object manipulation. Healthy adults also have highly effective reactive responses during grip tasks. In the event of prediction errors (or unexpected perturbations) the internal model can be briskly updated in response to sensory information obtained on contact and during movement of the object, with few lift repetitions required for grip to return to normal force-load profiles (Johansson et al. 1999; Johansson et al. 1992). Healthy adults are able to accurately control grip in response to externally imposed constraints, such as meeting a target force level during a force tracking task; errors between the target and force traces are small and plateau within few repetitions of the tracking task (Kurillo, Goljar, & Bajd, 2005b; Kurillo, Gregoric, Goljar, & Bajd, 2005).

2.2.4 Constraints on grip control in healthy adults.

While the hand has a large number of mechanical degrees of freedom, independent finger movement is constrained to some extent by structural arrangements and the organisation of neurological control, resulting in a phenomenon known as enslaving; where the action of one finger will cause involuntary movement in an adjacent finger. The effect of enslaving is beneficial in healthy adults as it ensures quick control of grip (Schieber & Santello, 2004). In addition to structural and neurological constraints, task constraints and the effects of aging may impact grip control.

Mechanical limits to the extent to which fingers can move independently are provided by the connections between the tendons and connective tissues and lumbrical muscle origins, in addition to the soft tissues and web spaces of the hand (Keen & Fuglevand, 2003; Von Schroeder & Botte, 1993, 1997; Von Schroeder, Botte, & Gellman, 1990). Central and peripheral neurological constraints on finger movement arise from neural output from the cortex to the spinal motoneuron pool; a single

motoneuron may innervate muscle fibres acting on one digit or on more than one digit. Pairs of motor units within the same muscle and across different muscles of the hand fire in synchrony; the similar time course of discharge of action potentials suggests common neural input to the motoneuron pools acting on different fingers (Reilly & Schieber, 2003). This common input assists appropriate timing of force production, and is most pronounced in the thumb and index finger and during power rather than precision tasks (Winges, Johnston, & Santello, 2006; Winges & Santello, 2004). Enslaving allows close coordination of finger forces, which when required can be modified enabling the fingers to operate more independently (Danion, Latash, & Li, 2003; Danion, Li, Zatsiorsky, & Latash, 2002; Winges et al., 2006). This permits, for example, in-hand manipulation of objects or release of a single finger during grasp.

In addition to mechanical and neural determinants of finger action during grasp, task constraints will impact the amount of force produced by the hand and individual digits. During multi-digit grip, finger forces will counterbalance the forces produced by the thumb in order to prevent the object from slipping (Winges et al., 2006). The amount of force required to be produced by each finger will depend on the type of grip, as the digits opposite the thumb are required to produce the greatest grip force. For example, the ring and little fingers are essential contributors (with the thumb) to a spherical grip task such as unscrewing a jar lid or turning a door knob (Kinoshita, Murase, & Bandou, 1996; Pylatiuk, Kargov, Schulz, & Doderlein, 2006), whereas the middle and index fingers are more involved in a cylindrical grip task such as holding a bottle and pouring (Pylatiuk et al., 2006).

2.2.5 Aging and grip control.

Grip strength progressively reduces with age, particularly from the fifth decade onwards (Bohannon et al. 2006; Mathiowetz et al. 1985; Ranganathan et al. 2001). Not all muscles are affected equally. In women, the decline in wrist and finger flexor strength starts from the fourth decade, while wrist extensor strength declines significantly from 60 years onwards (Christ et al., 1992). Grip control also changes as a function of normal aging in the absence of pathology. While predictive control of grip timing is maintained, grip force scaling may be impaired with increased amount of grip force used (Cole, Rotella, & Harper, 1998). Healthy older adults are significantly less accurate at force tracking tasks compared to younger adults (Kurillo, Gregoric et al., 2005; Shim et al., 2005). Tactile sensitivity in the fingers and hand is one contributor to these changes (Ranganathan, Siemionow, Sahgal, & Yue, 2001); however, this alone does not explain the changes in grip control in older adults (Cole et al., 1998). Neurological pathology such as stroke is more prevalent in older adults (Ministry of Health, 2008); impairments in grip control following stroke may therefore be compounded by pre-existing age-related decline in grip function.

2.2.6 Cortical activation during grip in healthy adults.

Diverse regions within the healthy brain are involved in planning and executing grip tasks. The primary motor cortex (M1), directly connected to the spinal motoneuron pool by the corticospinal tract, is the main driver for generating hand movement (Schieber & Santello, 2004). Representation of hand and finger muscles and movements are not localised but repeated throughout M1. M1 neurons diverge to innervate multiple intrinsic and extrinsic hand muscles, and multiple M1 neurons may converge in the

same intrinsic or extrinsic hand muscle (Schieber, 1999; Schieber & Hibbard, 1993; Schieber & Santello, 2004). Cortical involvement during hand tasks in healthy adults is not purely unilateral; activation of M1 during unilateral hand tasks, as well as generating movement in the contralateral hand, will evoke inhibition of the ipsilateral M1 (Classen, Liepert, Wise, Hallett, & Cohen, 1998; Duque et al., 2007; Ferbert et al., 1992; Kujirai et al., 1993). This inhibition enables unwanted movements to be suppressed.

M1 does not operate in isolation and motor output is dependent on the ability to process and interpret sensory input in conjunction with accessing and interpreting memory and planning the motor action. Integration of sensation, coordination of movement and motor learning involved with grip tasks involves sub-cortical regions (Castiello, 2005; Prodoehl, Corcos, & Vaillancourt, 2009). The premotor and parietal cortices are also involved during grip tasks (Lundy-Ekman, 2007; Nowak, 2008). The extent and intensity of activation in these regions is task dependent; increased grip precision results in increased cortical demands in healthy adults (Kuhtz-Buschbeck, Ehrsson, & Forssberg, 2001). When required to maintain grip just above the slip threshold, cortical activity in the contralateral primary sensorimotor cortex, supplementary motor area, cingulate motor area, ventral premotor cortex and parietal Brodmann areas increased compared to when required to use self- selected comfortable and firm grips (Kuhtz-Buschbeck et al., 2001). Increased cortical activation during grip control in healthy adults is not solely a function of the amount of force used but also the attention required by the task (Carey et al., 2006; Ehrsson, Fagergren, & Forssberg, 2001; Ehrsson et al., 2000; Pearce & Kidgell).

2.2.7 Grip control in healthy adults summary.

Grip control in healthy adults is highly efficient, but accuracy and scaling ability reduce with age. Feed-forward control mechanisms permit an object's properties to be accurately anticipated prior to grip. Just enough force is used when holding an object, with little risk of it slipping or being crushed. The central and peripheral organisation of finger movement contributes to this close coordination of grip with load forces. In light of this highly complex coordination of sensation, memory and movement, it is unsurprising that diverse cortical and sub-cortical areas are involved in even simple grip control tasks.

2.3 Grip control following stroke

2.3.1 Introduction.

Impairments of grip strength, scaling and timing of grip force and alterations to selective finger movement alter grip control following stroke. A lesion anywhere in the sensory and motor cortices is likely to impact hand function, and while the contralesional hand may be the most affected, dexterous function in both hands will be impaired (Hermsdörfer, Laimgruber, Kerkhoff, Mai, & Goldenberg, 1999; Nowak, 2008; Nowak, Grefkes et al., 2007; Quaney, Perera, Maletsky, Luchies, & Nudo, 2005). Accordingly, in this review the contralesional hand will be described as 'more affected' and the ipsilesional hand described as 'less affected'.

2.3.2 Grip weakness following stroke.

There are often significant reductions in grip strength in the more affected hand following stroke when compared with the less affected hand or with age-matched

controls (Blennerhassett, Carey, & Matyas, 2006a; Hermsdörfer, Hagl, Nowak, & Marquardt, 2003; Kamper, Fischer, Cruz, & Rymer, 2006; Li, Latash, Yue, Siemionow, & Sahgal, 2003; Warabi, Inoue, Noda, & Murakami, 1990). Impairments in grip strength correlate with reduced functional ability (Boissy, Bourbonnais, Carlotti, Gravel, & Arsenault, 1999; Mercier & Bourbonnais, 2004; Nowak, Grefkes et al., 2007). In conjunction with reduced ability to voluntarily activate muscle in direct consequence of the lesion, weakness may arise from disuse of the more affected hand contributing to muscle atrophy (Gracies, 2005; Pang & Eng, 2005).

The ability to grip successfully is not a function of strength alone, and may still be impaired where absolute maximum grip force production is not significantly different from healthy adults (Robertson & Jones, 1994). This is because somatosensory as well as motor deficits result from stroke, even if the lesion is confined to the motor cortex (Kim & Choi-Kwon, 1996; Nudo, Friel, & Delia, 2000). The degree to which tactile sensitivity is intact is a key factor in determining whether stable grip of an object can be successfully attained and maintained (Blennerhassett, Carey, & Matyas, 2006b; Hermsdörfer et al., 2003; Nowak, Hermsdörfer, Marquardt, & Topka, 2003; Robertson & Jones, 1994). However, diminished sensation does not always mean reduced ability in functional tests, demonstrating the complexity of assessing impairments in function and in grip control (Robertson & Jones, 1994). The ability to activate extrinsic as well as intrinsic hand muscles appropriately is an important contributor to successful grip. When muscle activation was recorded by electromyography (EMG) during a grip task, muscle activity was found to be significantly diminished in the extrinsic hand and finger muscles (both flexors and extensors) of people with mild chronic stroke compared to their intrinsic hand muscles (Grichting, Hediger, Kaluzny, & Wiesendanger, 2000).

Muscle activity in the intrinsic hand muscles was not significantly different from that of healthy controls during the task (Grichting et al., 2000).

2.3.3 Impairments in timing and scaling of grip force following stroke.

Force levels in excess of the safety margin are used by stroke survivors to grip, hold and transport an object (Hermsdörfer et al., 2003; Nowak et al., 2003; Wenzelburger et al., 2005). Ineffective central processing and integration of sensory feedback from the fingers results in higher grip forces as a compensatory strategy (Nowak & Hermsdörfer, 2005). The strategy of excessive grip force is not consistently successful. During isometric hold, grip forces often fluctuate, increasing the risk of grip failure (Blennerhassett et al., 2006; Nowak & Hermsdörfer 2005). In addition, this poor grip economy is likely to result both in rapid muscle fatigue (as grip strength is already reduced) and diminish the ability to perform fine finger movement during grip tasks (Hermsdörfer et al. 2003; Nowak et al. 2003).

Following stroke, peak grip and peak load forces are not closely coordinated. The timing of force modulation is frequently impaired, with a longer period of time taken to stabilise grip and generate maximum grip force when lifting an object (Wenzelburger et al., 2005). The ability to grade force of grip quickly and appropriately in response to anticipated and unexpected perturbations to load is also reduced (Grichting et al., 2000; Hermsdörfer et al., 2003; Mai, 1989; Nowak, Hermsdörfer, & Topka, 2003). Deficits in timing and scaling of force impact stroke survivors' ability to grade force appropriately during static grip control tasks such as force target tracking, resulting in significantly less accurate modulation of grip force compared to healthy controls (Kriz, Hermsdörfer, Marquardt, & Mai, 1995; Kurillo, Gregoric et al., 2005; Kurillo, Zupan, & Bajd, 2004).

2.3.4 Impairments in selective finger movement following stroke.

Reduction in selective muscle activation and independent finger movement is a feature of hand impairment following stroke, and independent finger movement is slow to recover (Kwakkel, Kollen, & Wagenaar, 2002). In particular, following mild stroke, the ability to independently move and produce force in the middle, ring and little fingers was found to be significantly impaired, more so than the thumb and index fingers (Lang et al. 2003; Li et al. 2003). Following moderate stroke, the effect on specific digits is more variable (Raghavan, Petra, Krakauer, & Gordon, 2006). Some movements may be more affected than others; abduction and adduction of a finger elicits activation in other muscles and fingers to a greater extent than flexion and extension movements (Lang & Schieber, 2004). While some enslavement contributes to efficiency of finger interaction and grip in healthy adults, the greater reduction in selective muscle activation following stroke is significantly associated with poorer functional task performance (Lang & Schieber, 2004). Cortical changes of reduced inhibition and peripheral changes of muscle shortening may contribute to the loss of selective finger movement (Gracies, 2005).

2.3.5 Cortical activation during grip following stroke.

As is apparent from studies of brain activity in healthy controls, diverse cortical regions are involved in planning and executing grip. The impact of stroke on grip function appears to be the same whether the lesion involves the right or left hemisphere (Nowak, Grefkes et al., 2007; Quaney et al., 2005). As well as affecting motor output, a cortical or sub-cortical lesion will impair sensory processing and sensory-motor integration (Kim & Choi-Kwon, 1996; Nudo, 2007; Nudo et al., 2000). Lesions in the

cerebellum (Hermsdörfer et al., 2003; Hermsdörfer et al., 2005; Nowak, Topka, Timmann, Boecker, & Hermsdörfer, 2007) and basal ganglia (Wenzelburger et al., 2005) disrupt both the planning and execution of grip tasks.

Following stroke, excitability of M1 in the lesioned hemisphere is reduced, decreasing descending corticospinal output and resulting in paresis (Brouwer & Schryburt-Brown, 2006). In transcranial magnetic stimulation (TMS) studies, reduced excitability in the lesioned hemisphere is evidenced by increased thresholds to elicit a response in target muscles, reduced size of motor response (reduced MEP amplitude) and increased time to elicit a motor response following cortical stimulation (prolonged MEP latency) compared to healthy adults (Turton, Wroe, Trepte, Fraser, & Lemon, 1996). Due to less inhibitory output from the lesioned side cortical inhibition of the non-lesioned M1 reduces, reducing the threshold for recruitment of excitatory neurons in the non-lesioned hemisphere (Bütefisch, Netz, Wessling, Seitz, & Hömberg, 2003; Murase, Duque, Mazzocchio, & Cohen, 2004). The net increase in excitability of the non-lesioned hemisphere drives further inhibition of the damaged hemisphere, and in consequence further reduces both excitatory output to the muscles of the more affected hand, and inhibitory output to the non-lesioned M1 (Liepert, Bauder, Miltner, Taub, & Weiller, 2000; Liepert, Hamzei, & Weiller, 2000).

2.3.6 Grip control following stroke summary.

Neural changes following stroke result in impaired timing and scaling of grip force and reduced accuracy during grip control tasks. Weakness and loss of selective finger movement due to central and peripheral changes may hamper effective grip control. Loss of descending output and asymmetry in the balance of excitability and

inhibition between the lesioned and non-lesioned hemispheres contribute to these changes in grip control following stroke.

2.4 Recovery of grip control following stroke

2.4.1 Introduction.

Increasing cortical excitability in the lesioned hemisphere, or reducing the level of inhibition from the non-lesioned hemisphere, provides a theoretical basis for interventions directed at improving grip control following stroke (Liepert, Graef, Uhde, Leidner, & Weiller, 2000; Liepert, Hamzei et al., 2000; Rossini et al., 2007). The potential for function to improve following neurological injury is dependent on the ability of neural structures to adapt. This process of neural reorganisation will be discussed, along with studies that have assessed recovery of grip control using objective measures.

2.4.2 Neuroplasticity.

Following unilateral stroke, metabolism and blood flow reduce distant to the site of lesion and in both hemispheres (Andrews, 1991). These changes, known as diaschisis, may persist beyond the acute phase following stroke. The extent to which diaschisis persists following cortical injury impacts whether functional improvement is due to 'true' recovery or to the ability of the brain to be plastic; that is, for regions adjacent to and distant from the lesion to adapt and adopt the functions previously performed at the site of the lesion (Nudo, 2007; Nudo, Plautz, & Frost, 2001).

Neuroplasticity is the term used to describe non-momentary changes in neurotransmitter production and the function and structure of neurons (Kleim & Jones, 2008; Nudo et al., 2001; Woolf & Salter, 2000). In the central nervous system the mechanisms for change include: sprouting new axons and neural connections, unmasking existing but latent horizontal connections, and increasing synaptic efficiency of pre-existing functional connections (Caramia, Iani, & Bernardi, 1996; Hess & Donoghue, 1994; Sanes & Donoghue, 2000). Neuroplasticity occurs spontaneously around damaged tissue following cortical injury and during recovery. Neuroplastic changes can also be induced in undamaged tissue following functional compensations made for the injury, but also in response to sensory input and training. For example, increased cortical activity in diverse brain regions is observed while healthy adults are learning a new skill. The regions of the brain active during the task become fewer and smaller in area as the skill is successfully acquired (Meister et al., 2005). Persistent training can however result in a permanently enlarged motor representation in healthy adults compared to the untrained hand (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995). Neuroplasticity will occur unaided, but if positive cortical and beneficial functional changes are desired, motor skill learning (rather than repetitive practice of non-meaningful tasks), appears central to maximising neurological and functional improvements (Kleim & Jones, 2008; Plautz, Milliken, & Nudo, 2000).

When plasticity following stroke in relation to grip tasks is considered, people who have experienced a stroke have reduced excitability of M1 in the lesioned hemisphere compared to healthy controls, whether measured by amplitude or the area of evoked response during grip tasks. In addition, activation of secondary motor regions such as the pre-motor cortex and supplementary and cingulate motor areas is increased

(Cramer et al., 1997). However, changes in cortical excitability are not confined to secondary areas in the same hemisphere as the lesion. Secondary areas become increasingly utilised in both hemispheres during grip tasks following stroke when there has been significant damage to M1 (Hamzei, Liepert, Dettmers, Weiller, & Rijntjes, 2006; Tecchio et al., 2006; Ward et al., 2007). Reduced efficiency of these secondary areas, in both hemispheres, for performing grip tasks is reflected in poorer performance of these participants in functional tests compared to those who have greater M1 excitation in the lesioned hemisphere during the task (Teasell, Bayona, & Bitensky, 2005; Ward et al., 2007; Ward et al., 2006). Similarly, an increase of excitability in the lesioned M1 during grip tasks, i.e. redressing the balance of interhemispheric excitability, is associated with improved hand function (Rossini et al., 2007; Ward et al., 2007). While less efficient, recruiting secondary motor and sensory areas not normally involved in a task is evidence of the role of neural plasticity, demonstrating the spread of cortical activity to novel areas in an effort to regain function lost following stroke (Tecchio, 2006).

The propensity for diverse areas of M1 to be involved in finger movement, with hand muscles and movements represented in diffuse, repeated and overlapping regions, provides the opportunity for functional recovery via cortical reorganisation when there is damage to one part of the cortex or descending pathways (Schieber, 1999; Schieber & Hibbard, 1993; Schieber & Santello, 2004). The objective of stroke rehabilitation strategies is therefore to promote positive neuroplastic change.

2.4.3 Interventions to improve grip control following stroke.

A small number of studies have investigated interventions to improve grip control following stroke. These studies used a range of study designs and interventions

and measured different aspects of grip control in addition to functional measures. Of these, only one study assessed the effects of the intervention on measures of cortical excitability.

Engaging the cortex by voluntary movement during task specific training and increasing afferent input from the periphery are strategies aimed at increasing and altering afferent input to effect organisational change in the cortex (Bhatt et al., 2007; Kleim & Jones, 2008). In one high quality randomised controlled trial (McDonnell, Hillier, Miles, Thompson, & Ridding, 2007), ten people with sub-acute stroke received one hour of peripheral nerve stimulation prior to engaging in task specific upper limb training for an hour, while the control group received sham stimulation and the same amount of training. The peripheral nerve stimulation was applied at sufficient intensity to provoke a motor response in the first dorsal interosseous and abductor pollicis brevis muscles. Stimulation was passive, with both groups instructed to attend to their resting stimulated hand. The training activities were targeted to the individual, determined by assessment of each participant's impairments and functional goals. After three weeks of three sessions per week training (in addition to a home exercise programme) no significant changes were found in cortical excitability in the hand motor area of the lesioned hemisphere over time or between the two groups as measured by TMS. However, grip control improvements were evident in both groups with significantly reduced time to establish stable grip (reduced pre-load duration) and increased peak grip load force rates during a precision grip-lift task with the index finger and thumb. The improvements in grip force scaling were significantly greater in the group that received peripheral stimulation prior to task training. Improvements in Motor Activity Log Amount of Use score for the affected hand, tapping speed and maximum pinch strength

improved in both groups but with no significant difference between them. These changes, including the lack of change in measures of cortical excitability and between group differences in grip scaling, persisted at three months follow up. The authors attribute the lack of change in measured cortical excitability to the participants having consolidated the skills learned during training. If this is the case, as the TMS measures were not taken during the intervention period, any short-term changes in cortical excitation that may have been apparent at earlier stages of training would not be captured. In addition, as discussed above in chapter 2.4.2 and further in chapter 2.5.5, if changes in cortical excitability were occurring elsewhere than the lesioned M1, TMS of the lesioned hemisphere would not be able to identify these changes. While the results of this study provide good evidence that peripheral stimulation prior to progressive task specific training improves grip control more than training alone in these participants with sub-acute stroke, any cortical changes that may have occurred in conjunction with this improvement remain unknown.

In a smaller randomised controlled trial, ten patients three to nine months post-stroke were assigned to immediate or delayed treatment groups. The immediate group received constraint induced therapy; for two weeks the less affected hand was placed in a mitt for 90% of waking hours in addition to six hours per day five days per week of task training (Alberts, Butler, & Wolf, 2004). The delayed treatment group acted as the control and received no therapy. In order to participate in constraint induced therapy, a minimum level of hand movement (20 degrees active wrist extension, 10 degrees active finger extension and 90 degrees active shoulder flexion and abduction) was required. In addition to functional tests (Wolf Motor Function Test, Fugl-Meyer Assessment; Hand and Arm section) and maximal grip force, grip control was tested using a key-turning

task. Despite the intensity of training, no statistically significant differences in functional performance were found post-intervention; performance on the Wolf Motor Function Test was variable (some increased, some decreased performance time). There was a trend for reduced time to establish grip in the immediate treatment group. Inconsistent force profiles during the key turning task measured prior to constraint induced therapy became smoother post-intervention, showing improved increase and decrease of grip contemporaneously with changes in load forces. The study highlights that increases in maximum strength do not necessarily result in improvement in grip control or functional tasks; while one participant's maximal pinch strength improved by 128 % following constraint induced therapy, they remained unable to perform the key turning task.

The remaining studies do not employ a randomised controlled trial design. Additional afferent input was provided to the forearm by light touch of the contralateral hand or by resting the arm on a skateboard during a grip and lift task in six people with acute stroke (13 - 33 days post stroke) and compared their performance with that of six healthy controls (Aruin, 2005). For the healthy controls and the participants with stroke there was an immediate significant effect of providing additional sensory input in reducing both the excessive grip forces used and the time to reach peak grip force during the grip-lift task. These results suggest that provision of additional sensory input to the arm (that did not affect the stability of the hand) may have immediate effects in improving grip control.

Two studies employed case study designs to investigate the effect of robot training using the Hand Mentor in conjunction with repetitive task practice. The Hand Mentor is a robotic exoskeleton that assists passive movement, can be set to resist wrist

and finger movement and provides visual feedback of muscle activity via EMG-electrodes. In the first case study, the participant was seven months post stroke and received two hours of training with the Hand Mentor and two hours of repetitive task practice three days a week for three weeks (Frick & Alberts, 2006a). Mean maximal grip strength reduced in the more affected hand after the three week intervention. No explanation was provided as to why the participant's strength reduced following the intervention. Conversely, mean Wolf Motor Function Test time improved by 34.6% after the intervention, with greater percentage improvements in time to complete the dexterity components of the test. Grip control was measured as the participant's ability to maintain a stable force output for ten seconds during maximal grip. Post-intervention, the force-time profile smoothed. The authors propose from these results that the improvement in function resulted more from improved grip control than increased strength, and improvement was possible in the face of the participant's continued sensory deficits.

The second case study using the Hand Mentor assessed changes in Wolf Motor Function Test, Motor Activity Log and Fugl-Meyer Assessment in a participant who was 11 months post stroke (Rosenstein, Ridgel, Thota, Sarnarne, & Alberts, 2008). The training protocol was the same as that used by Frick and Alberts (2006), however the measure of grip control was novel; assessing the forces produced while separating two transducers using a precision grip. At pre-intervention, while the participant was able to generate sufficient gross force to separate the two transducers (5 N), lack of coordination of the forces produced by the two hands meant she was unable to pull the transducers apart. At post-intervention, while there were some improvements in the time to perform some gross movement items in the Wolf Motor Function Test, this was not

consistent across all movements, and the participant remained unable to perform the dexterity components of the test. However, the participant was sufficiently able to coordinate stabilising the less affected hand and producing force with the more affected hand in order to pull the two transducers apart, and the force time profile was smoothed showing improved coordination of grip force in response to the load. This study did show positive changes in grip force stability in a participant with severe stroke, whereas the other studies considered here have included participants with mild to moderate impairments.

No assessment was able to be made in either study using the Hand Mentor as to whether it was the repetitive task practice or robot assisted therapy or the two interventions combined that prompted the changes in grip control.

The final two studies used force tracking training tasks as an intervention to improve grip control. These studies combine repetitive practice of the grip control task (tracking a force trace) with visual feedback of performance. The first study investigated the effects of repeated tracking training for 10 - 15 minutes per day, 4 - 5 times per week for four weeks in ten participants in the sub-acute stage following stroke (Kurillo, Gregoric et al., 2005). This training was in addition to any standard physiotherapy the participant was receiving. Using a multi-digit grip on a force handle, participants were required to trace ramp, rectangular and sine wave targets as accurately as possible. Target amplitudes ranged between zero N (complete release) and 30% of each participant's maximal grip strength; grip strength was assessed prior to each training session and the trace targets adjusted accordingly. Eight out of ten participants significantly reduced their tracking error following training; the two who did not

improve in tracking accuracy were the eldest (79 years) and the most chronic (six years since stroke) participants.

The second force tracking study assessed a precision grip tracking task in ten participants with brain lesions of various origin, including five participants with stroke, at different stages (sub-acute to chronic) since injury (Kriz et al., 1995). Participants performed 36 repetitions of ramp tracking tasks during weekly sessions of 30 minutes for a maximum of ten weeks. Performance was assessed pre- and post-intervention during five repetitions of each of a regular sine wave and a randomly generated sine wave task. Target amplitudes for all tasks ranged between 2.5 and 7.5 N. Pre-intervention, all participants had high grip force amplitudes indicating force overshoot in all tasks. All but one of the stroke participants reduced tracking error at post-intervention, and all but one of the stroke participants reduced their tracking error at post-intervention to within the range of the healthy controls tested using the same protocol.

In contrast with the preceding studies that sought to improve grip control by interventions aimed at the hand, the final study showed grip control may be altered by direct modulation of cortical excitability (Dafotakis et al., 2008). Twelve participants, who had sub-acute sub-cortical strokes, received a single episode of ten minutes of 1 Hz repetitive TMS (rTMS) over M1 of the non-lesioned hemisphere, at 100% of the resting threshold for the first dorsal interosseous muscle. This intervention was effective in improving a number of aspects of grip control in the more affected hand during a precision grip-lift task immediately post-intervention. Peak grip forces reduced and the ratio of grip to load force reduced, indicating better approximation of the grip force used to the demands of the load. Timing of grip force also improved; the time-lag between

grip and lift forces shortened post-intervention. There was no change in performance in the less affected hand following rTMS. The authors assert the results support the theory of interhemispheric competition (Ferbert et al., 1992), in that the inhibitory effect of rTMS on the non-lesioned M1 unmasked excitability in the lesioned hemisphere. The study did not include any measures assessing cortical excitability changes, therefore any cortical origins or associations with the improvement in grip control are unknown. As there was no assessment of the duration of the effects, and application of the treatment was to people with sub-cortical stroke alone, the longevity of positive treatment effects and the benefit of this intervention for other populations with stroke are likewise unknown at this stage.

2.4.4 Recovery of grip control following stroke summary.

Of these few studies that have investigated the effects of interventions on grip control following stroke, all have had small sample sizes and most have assessed the effect on people with mild to moderate stroke. There is good evidence, however, that providing additional afferent input to a target muscle prior to training improves grip control to a greater extent than the training alone (McDonnell et al., 2007); the resulting improvements in grip control in people with stroke may occur in the absence of evidence of changes in cortical excitability that have been seen in healthy populations (see chapter 2.5.5. below). While the results of the non-randomised controlled trial studies cannot be given the same weight due to their experimental design, a common theme emerging is that providing repetitive practice of grip control tasks or functionally relevant tasks appears to improve the scaling of grip control as indicated by smoothing of force profiles and improved grip force accuracy when tracking a target. The results of these studies highlight that maximal grip strength may not be closely related to grip

control (whether measured objectively using grip-lift or force tracking tasks or indirectly through functional task performance). This demonstrates both the complexity of the relationship between strength, function and grip control and the importance of assessing and treating impaired grip control separately from strength.

2.5 Neuromuscular electrical stimulation

2.5.1 Introduction.

Prior stimulation of a target muscle can improve grip control (McDonnell et al., 2007). An intervention commonly used clinically is neuromuscular electrical stimulation (NMES) either in isolation or in conjunction with movement and functional tasks. The physiological effects of NMES will be discussed, providing the conceptual basis for using NMES. In particular, NMES triggered by EMG activity in the target muscle will be discussed as a possible means of increasing cortical excitability and improving grip function. A small number of studies have assessed the neural effects of EMG-NMES in people with stroke using functional magnetic resonance imaging (fMRI). NMES parameters vary between studies and the rationale for choice of NMES parameters is often not stated. The basis for using wide pulse width and high frequency NMES settings as a means of reducing possible fatigue associated with NMES will be explored.

2.5.2 NMES - physiological and theoretical rationale.

NMES is one intervention designed to induce changes in motor function by providing a peripheral stimulus to elicit or assist contraction of paretic muscles. The

physiological rationale behind NMES is that motor axons in the proximity of the surface electrodes applied over the target muscle are directly activated by electrical stimulation, passively evoking a muscle contraction (passive NMES) or working in conjunction with active contraction of the stimulated muscles by the patient (active NMES) or during a task (functional NMES). A refinement of active or functional NMES is NMES coordinated with EMG and programmed to provide stimulation only once a threshold level of voluntary activation of the target muscle is reached (EMG-NMES).

Muscle activation induced with the assistance of NMES is thought to increase proprioceptive signals, increasing the size and strength of projections from the muscle to the sensory and motor cortices, thereby increasing cortical excitability (Sheffler & Chae, 2007). As EMG-NMES works in concert with voluntary movement, the application of EMG-NMES may therefore enhance any change in cortical excitability that occurs during voluntary movement alone.

While there are as yet no published studies on the functional effects of passive NMES compared to EMG-NMES following stroke, passive NMES compared to functional NMES has been compared in one study. Participants with severe stroke received a total of 5 hours of functional NMES evoking wrist and finger flexion or extension when triggered by a therapist during a grasp and release task. The functional NMES protocol was compared to the same duration of passive NMES of the finger flexors and extensors (Santos, Zahner, McKiernan, Mahnken, & Quaney, 2006). Effects of the different modes of NMES on cortical excitability were not assessed. While both groups significantly improved in Fugl-Meyer Assessment score and there were no significant between-group differences, the functional NMES group alone improved significantly in Box and Block Test score and Jebsen Taylor Hand Function Test time.

This showed a trend for greater improvement in functional performance when NMES was used in conjunction with an active task rather than used passively. These results provide a basis for preferring as an intervention a modality that increases afferent input and assists goal directed voluntary movement during a functional task as a means to facilitate neuroplasticity and functional improvement (Kleim & Jones, 2008).

2.5.3 NMES and wrist and finger flexor stimulation.

Of the studies that have employed NMES as an intervention following stroke, the majority have applied the stimulation to wrist and finger extensors alone (Cauraugh et al. 2002; Cauraugh et al. 2003a; Cauraugh et al. 2003b; Cauraugh et al. 2005; Cauraugh et al. 2000; Francisco et al. 1998; Hara et al. 2006; Kimberley et al. 2004; Page et al. 2006; Powell et al. 1999). Two studies have looked at the effect of alternating stimulation to finger flexor and extensor muscles. Passive NMES to the wrist extensors for 6 weeks compared to passive NMES applied alternately to wrist flexors and extensors did not result in any significant difference in any impairment or functional outcome measure in a population with chronic stroke (de Kroon, Ijzerman, Lankhorst, & Zilvold, 2004). As discussed earlier, alternating stimulation of flexors and extensors (triggered remotely by the therapist, not EMG) during a functional activity had a more beneficial effect on most outcome measures used than passive NMES of the same muscle groups (Santos et al., 2006). Adding volitional activation of the muscle to the protocol may be more important than which muscle groups are stimulated.

2.5.4 NMES and grip control.

Most studies using NMES (on any muscle group) have measured any effects through change in performance on functional tests or the ability to produce maximal

force by testing maximum grip and isometric finger strength. Objective measures of grip control are rarely used. One group of studies (Cauraugh & Kim, 2002, 2003a, 2003b) has assessed the effect of EMG-NMES on the ability to reduce force variability during an isometric wrist extension task. In these studies EMG-NMES was applied unilaterally, assisting movement of the wrist and finger extensors of the more affected hand. This was compared to a bilateral training programme of EMG-NMES of the more affected hand in conjunction with active extension of the less affected hand. Following six hours of EMG-NMES training over two weeks, participants in both the unilateral and bilateral training groups showed increased ability to maintain a stable force level (shown by significantly reduced variability during sustained maximal contraction of the wrist and finger extensors), as compared with controls performing active extension of the wrist and fingers without NMES (Cauraugh & Kim, 2003a). While the authors' outcome of interest was maximal force production during an isometric task, these results suggest EMG-NMES in conjunction with voluntary activation may have a beneficial effect on reducing the variability of force produced by the hand. This finding is relevant for the current study, as reducing the high variability in grip forces seen following stroke may assist in improving grip control.

2.5.5 Central effects of NMES and peripheral nerve stimulation.

The studies addressed so far have focused on the effects of NMES at an impairment and functional level. The studies discussed in this section identify the cortical effects of applying electrical stimulation via EMG-NMES or peripheral nerve stimulation in healthy adults and following stroke.

Central effects of NMES in healthy adults - evidence from transcranial magnetic stimulation studies

In one study, two minutes of low frequency active wrist extension followed by relaxation was found to increase cortical excitability of wrist extensors momentarily, whereas the same duration of sustained isometric wrist extension, alternating active wrist extension and flexion or passive NMES of the wrist extensors had no statistically significant in healthy adults (Hauptmann, Skrotzki, & Hummelsheim, 1997). The authors suggested alternating muscle group action probably had an inhibitory effect on the muscles of interest (in that case the wrist extensors) resulting in no short term changes in cortical activity. Immediate increases in cortical excitability in the contralateral hemisphere have been found following short duration EMG-NMES applied to the wrist and finger extensors and following active movement of the wrist, but not following passive NMES (Taylor, Lewis, Taylor, & Rosie, 2008).

Central effects of NMES following stroke – evidence from functional magnetic resonance imaging studies

Twenty participants who had a stroke at least six months previously were randomly assigned to one of three groups: a) movement tracking training task using the index finger, b) EMG-NMES of the finger and wrist extensors or c) training that combined EMG-NMES with finger tracking training (Bhatt et al., 2007). In the combined training group, finger tracking practice was performed during stimulation rest periods. After ten one-hour sessions over 2-3 weeks, Box and Block Test score and Jebsen Taylor Hand Function Test time improved significantly in both the stimulation and combined training groups, without significant differences between the two groups.

There was no significant improvement in these tests over time following finger tracking training alone. Changes in cortical excitability were assessed using fMRI. Within- and between-group comparisons showed combining finger tracking training with EMG-NMES did not result in changes in cortical activation compared to either training task alone with respect to blood oxygenation level dependent (BOLD) signal intensity (a measure of the intensity of activation) in either the lesioned or non-lesioned hemisphere, consequently there was no change in laterality index (a ratio of the volume of activation in each hemispheres). When associations between changes in laterality index and BOLD signal intensity were assessed, improvement in function was positively associated with changes in cortical activation in the combined training group alone. Improved Box and Block Test score was positively associated with increased shift of activation to the M1, primary sensory cortex and premotor cortex in the lesioned hemisphere (as shown by the laterality index) and to reduced BOLD signal intensity in secondary areas, the primary sensory cortex and supplementary motor area, in the lesioned hemisphere. The functional improvement in the combined training group was therefore related to a normalisation of cortical excitability by hemisphere and intensity. This is consistent with other studies that have observed the positive association between cortical activity in the lesioned hemisphere and improved functional recovery (Rossini et al., 2007; Tecchio et al., 2006). As has been discussed in chapter 2.3.5 above, increased activity in M1 and reduced signal intensity in secondary areas in the lesioned hemisphere suggests increased efficiency of cortical processes following the combined training alone (Carey et al., 2007).

The effect of performing 30 minutes of EMG-NMES to the wrist and finger extensors twice a day, five times a week for ten weeks during ‘low intensity physical

activities' was assessed using fMRI, the Box and Block Test and an index finger tracking task in a group of participants with chronic stroke (Shin et al., 2008). Control participants performed the low intensity physical activities alone for the same duration. Accuracy during the tracking task and Box and Block Test scores improved significantly in the EMG-NMES group at post-intervention assessment and participants receiving EMG-NMES performed significantly better over time in all tasks than the controls. fMRI during active flexion and extension of fingers of the more affected hand identified changes in cortical activation in the EMG-NMES group post-intervention but not the controls. The cortical regions in which levels of activation changed post-intervention varied among the participants. Participants receiving EMG-NMES who at pre-intervention had unilateral activation of regions of the non-lesioned hemisphere or bilateral activation in both hemispheres, at post-intervention reduced in activation in the non-lesioned hemisphere and/or showed increased activation in the lesioned cortex. This shift in activation towards the lesioned side occurred in the sensorimotor cortex in six participants, in the pre-motor cortex in four participants and in the supplementary motor area in three participants. With these variable results in the EMG-NMES group, only the laterality index for the sensorimotor cortex was statistically significant in favour of improved activation of the lesioned hemisphere following training. Change in laterality index in the training group was positively correlated with improvement in Box and Block Test score and improvement in tracking accuracy in the training group.

In participants with chronic stroke, an intensive three week home programme of EMG-NMES for six hours a day was compared to a control group receiving sham stimulation during active finger movement for the same duration (Kimberley et al., 2004). EMG-NMES was applied to the wrist and finger extensors and combined with

passive NMES; participants in the NMES training group performed hand opening and closing repetitions assisted by the electrical stimulation. While strength in finger extensors improved significantly in the control group, the NMES training group alone had significant improvements in some items in the Jebsen Taylor Hand Function Test, Box and Block Test score and small but significant improvements in Motor Activity Log Amount of Use and How Well scores after the intervention. Cortical activation was measured pre- and post- intervention using fMRI during a finger movement tracking task. Accuracy of performance during the finger tracking task did not improve in either group. There was no change in either group in the number of active sites in either hemisphere. However, the intensity of cortical activation increased significantly in the intervention group alone in the non-lesioned primary sensory cortex; no changes occurred in M1 in either hemisphere. The lack of cortical demand required by the training task (as there was no problem solving or skill acquisition component) was attributed by the authors as the reason for the lack of change in cortical activation in the lesioned hemisphere. An alternative explanation was that, as the finger tracking task used during the fMRI did not duplicate the treatment task, changes in cortical activation as a result of the training may not have been captured by the use of the tracking task during measurement of cortical activation. However, the results from the study by Shin et al. (2008), discussed above, indicate that changes in cortical activation can be identified using fMRI without needing to duplicate the training task during assessment. In that study, increased cortical activation of regions of the lesioned hemisphere was identified by fMRI during a simple hand opening and closing task that differed from the training task, which combined EMG-NMES with functional tasks. Kimberley et al. (2004) recommended combining EMG-NMES with force tracking tasks, which would

be more cortically demanding, as a means of addressing the possible limitations of their study.

In summary, interventions between three and ten weeks in duration using EMG-NMES in conjunction with training requiring voluntary activation of the target muscles have been able to elicit increased cortical activation and functional improvements in participants with chronic stroke. The sites of cortical changes have been found to vary between individuals. Neural changes were on occasion occurring in secondary cortical areas and/ or the contralateral hemisphere in some individuals; changes in cortical activation were not always seen in the lesioned hemisphere or in M1.

2.5.6 Peripheral nerve stimulation and cortical excitability.

There are few studies that have considered the effects of NMES, applied over the muscle bellies to evoke or assist movement, on cortical excitability. A brief synopsis follows of studies that have investigated changes in cortical excitability following peripheral nerve stimulation in populations of healthy adults and following stroke.

Central effects of peripheral nerve stimulation in healthy adults

In healthy adults, applying peripheral nerve stimulation for two hours at intensities below the level of inducing movement increased cortical excitability of the regions of the motor cortex associated with the intrinsic hand muscles supplied by that nerve (Kaelin-Lang et al., 2002; Ridding, Brouwer, Miles, Pitcher, & Thompson, 2000). Peripheral stimulation of the radial and ulnar nerves was found to increase cortical excitability measured in healthy participants but only subsequent to receiving 45 minutes stimulation; increases in MEP amplitude in the first dorsal interosseous muscle

were not significant during the antecedent 15 minute intervals tested (McKay, Brooker, Giacomin, Ridding, & Miles, 2002).

Two hours of stimulation of the radial and ulnar nerves of healthy participants was compared to motor point stimulation of the first dorsal interosseous muscle in isolation or paired to coincide with cortical stimulation. Peripheral nerve stimulation intensity was sufficient to evoke weak contractions in first dorsal interosseous, abductor pollicis brevis and abductor digiti minimi (Charlton, Ridding, Thompson, & Miles, 2003). In most participants, each of the testing protocols resulted in intracortical facilitation in at least one of the three intrinsic hand muscles tested. Neural effects of peripheral stimulation varied widely between participants. Across all participants tested, stimulation of the peripheral nerve or motor point resulted in no change to cortical excitability in the contralateral hemisphere in some of the muscles tested, and depression of MEPs occurred in about a quarter of the results.

Using fMRI in healthy adults, prolonged peripheral nerve stimulation techniques has resulted in enlargement of novel regions in the contralateral sensorimotor cortex in addition to increased number of activated sites and BOLD signal intensity in M1 and premotor cortex during subsequent thumb movements (Wu, van Gelderen, Hanakawa, Yaseen, & Cohen, 2005).

Central effects of peripheral nerve stimulation following stroke

The same paradigm as used by Wu et al. (2005) has been applied with participants who have experienced a stroke (Sawaki, Wu, Kaelin-Lang, & Cohen, 2006). Cortical excitability was, however, measured using TMS not fMRI. Two hours of peripheral nerve stimulation preceded 30 minutes training of thumb movements. This resulted in a training-induced change in the direction of thumb movement in

participants with stroke comparable to the training effect on healthy controls, whereas movement training alone had no effect. Whereas in Wu et al. (2005) there were significant increases in cortical activity in the hemisphere contralateral to the moving hand, these motor training changes in the participants with stroke occurred in the absence of significant changes in cortical excitability in the lesioned hemisphere.

2.5.7 NMES parameters.

A recent Cochrane systematic review of the use of NMES to promote movement recovery or functional ability following stroke concluded that there was a statistically significant benefit of NMES over no treatment for some aspects of motor impairment and for improving functional ability (as measured by the Box and Block Test) (Pomeroy, King, Pollock, Baily-Hallam, & Langhorne, 2006). The authors cautioned that these conclusions were drawn mainly from single studies and the dose, frequency and duration of NMES varied between studies.

It has been suggested that NMES preferentially activates large diameter fast conducting axons that innervate fatigable fast twitch type II muscle fibres, and that this preferential activation of fatigable fibres (a reversal of the motor unit recruitment order that occurs during a voluntary contraction) contributes to increased muscle fatigue following NMES (Baldwin, Klakowicz, & Collins, 2006; Thomas, Nelson, Than, & Zijdewind, 2002). This hypothesis has been tested in healthy adults, where stimulation of lower limb muscles by NMES at 50 Hz resulted in slowing of direct motor responses as measured by M-wave latency, and speeding up of monosynaptic stretch reflex activation (reduced time to peak twitch force of H-reflex responses) (Trimble & Enoka, 1991). This suggests that, at least in healthy participants, fatigue resistant slow twitch type I muscle fibre recruitment is delayed and occurs at higher stimulation intensities;

therefore, NMES alters the population of motor units activated compared to voluntary contraction. Trimble et al. (1991) propose that strength gains associated with NMES in healthy adults are a result of this reversed order of motor unit recruitment, as muscle fibres that could only be activated with high intensity voluntary exercise can be trained with the assistance of NMES at lower intensities.

The neurophysiological effects of NMES have mainly been explored in healthy adults and/or in lower limb muscles. If fatigue resistant type I fibres atrophy following disuse after stroke, as has been suggested by some authors (Gracies, 2005; Hu, Tong, & Li, 2007; Kallenberg & Hermens, 2009; Toffola, Sparpaglione, Pistorio, & Buonocore, 2001), NMES protocols that preferentially target type II fibres may evoke increased muscle fatigue and reduce the range of force modulation available rather than provide an optimal training stimulus. One study has examined the activation order of motor units in response to electrical stimulation in the partially or fully paralysed thumb muscles of a small number of participants with spinal cord injury (Thomas et al., 2002). In most participants and motor units assessed, the reverse order of motor unit recruitment to that identified by Trimble et al. was found. In general, narrow diameter slow conducting axons were activated by high intensity median nerve stimulation (10 – 70 mA) prior to axons that innervate fast fatiguing muscle fibres. The authors concluded that as the order of activation of motor units under a superficial electrode will be affected by proximity to the electrode, axon diameter and axon excitability, the relationship between nerve stimulation and the order of motor unit recruitment was therefore mixed rather than hierarchical. From the general outcome of their study (showing similar order of activation to a voluntary contraction), an alternative explanation for the fatigue elicited following electrical stimulation was required.

Whether EMG-NMES will alter the recruitment order of motor units in a population with stroke is unknown. Altering the NMES stimulus parameters to wide pulse widths (0.5 -1 ms) at high frequency (approximately 100 Hz) activates sensory axons, stimulating motoneurons to be activated by spinal reflex pathways and eliciting muscle contractions via the smallest diameter axons that innervate fatigue resistant muscle fibres first (Baldwin et al., 2006; Dean, Yates, & Collins, 2007; Panizza, Nilsson, Roth, Basser, & Hallett, 1992). This may minimise the possibility of evoking excessive or premature fatigue. The effect of wide pulse width, high frequency stimulation has, however, only been assessed in healthy populations, and the outcome measure of interest in these studies has been change in the maximal strength of the target muscles. In one study, endurance was assessed in addition to strength. An immediate significant improvement in ability to maintain a sub-maximal contraction at 60% MVC in the highly fatigable muscle flexor digitorum brevis (in addition to increased maximal strength) was observed following a six week intervention using NMES (Marqueste, Hug, Decherchi, & Jammes, 2003). This suggests that the ability to sustain force output at a sub-maximal level, in addition to increasing peak force, may be enhanced by similar NMES protocols.

Protocols of high and low frequency NMES have been compared in one study (Baldwin et al., 2006). In wrist flexor muscles of healthy adults, wide pulse (1 ms), high frequency (100 Hz) NMES of the wrist flexor muscles was found to increase peak torque compared to low frequency (20 Hz) NMES. The benefits to torque production of using similar high frequency NMES protocols have been confirmed in studies of force production in the lower limb of healthy adults (Dean et al., 2007; Dean, Yates, & Collins, 2008). Comparisons of high and low frequency NMES on the ability to

maintain sub-maximal forces, as required during grip control, have not been conducted. Grip control requires effective and efficient responses to afferent inputs as well as sufficient force output. Whether targeting sensory Ia afferents by increasing frequency and pulse width of NMES parameters assists grip control or increases cortical excitation, in addition to increasing maximal force output, has not been assessed in healthy or neurologically impaired populations.

2.5.8 Neuromuscular electrical stimulation summary.

EMG-NMES can be used to provide increased afferent input and assist voluntary motor output to affected muscles following stroke. A single episode of NMES or peripheral nerve stimulation, while tending to increase MEP amplitude in target muscles in healthy adults more than resting or movement alone, may have variable effects on cortical excitability in both healthy participants and following stroke, particularly in respect of effects on the lesioned hemisphere. There is however evidence that following stroke, EMG-NMES can assist in rebalancing levels of cortical excitability between the hemispheres and these changes are seen in conjunction with improvements in dextrous hand function. As is apparent from the review presented here, the choice of stimulation parameters differs widely between studies. There is rationale for using wide pulse width high frequency NMES parameters on the basis of reducing the potential for fatigue associated with applying NMES, and enhancing afferent input by stimulating sensory axons rather than motor axons alone.

3 Method

3.1 Introduction

The purpose of this study was to assess the immediate effects, in terms of cortico-motor excitability and grip control, of a short intervention of EMG-NMES compared with voluntary activation of finger flexors in participants with chronic stroke. This chapter will set out the study design, participant details, methods, data management and statistical analyses applied in order to address this objective.

3.2 Sample size

The results from this pilot study will be used to inform power analysis in future related studies. For the purposes of this pilot study a pragmatic assessment of the number of participants required was applied, and no power analysis was performed. Recruiting continued until ten participants who were able to perform the cortical excitability component of the study were enrolled. This number is consistent with study population sizes in previous force tracking studies (Kurillo, Gregoric et al., 2005) and studies investigating cortical excitability (Bhatt et al., 2007; Conforto et al., 2008; Liepert, Graef et al., 2000) using similar methods to those employed here.

3.3 Study setting and design

All testing took place in the Health and Rehabilitation Research Centre, AUT University, Auckland. Participants were recruited via the Auckland branch of the

Stroke Foundation of New Zealand, the AUT University Neurological Physiotherapy Clinic and Neuro Rehab Results Limited (a neurological rehabilitation outpatient clinic), Auckland.

A within-subject design with experimental and control interventions was used. The study was unblinded as the researcher was involved in recruitment and delivery of the intervention. All participants were informed of the purpose and methods of the study verbally and in writing (see Appendix A) and gave written informed consent to take part in the study (see Appendix B).

Neural excitability and grip control were assessed in separate sessions for each of the intervention and control protocols; each participant was therefore required to attend the laboratory on four occasions. The order in which the testing occurred was randomised by use of a web based randomisation programme (www.random.org) prior to enrolment of each participant.

3.4 Ethical and cultural considerations

Ethics approval was obtained from the AUT University Ethics Committee (AUTEC), approval number 08/01 (see Appendix C). The principles of the Treaty of Waitangi of partnership, participation and protection were applied in the design and delivery of the study. All volunteers meeting the inclusion criteria had an equal opportunity to take part in the study regardless of ethnicity.

3.5 Study participants

3.5.1 Inclusion criteria.

Participants with unilateral stroke, cognitive capacity, residual grip ability and visual acuity were included in the study. Volunteers who had experienced a unilateral stroke six months or more prior to enrolment that affected the upper limb were eligible to participate. Volunteers were required to have the cognitive ability to follow instructions and to provide informed consent. This was evaluated by the telephone Mini-Mental State Examination (telephone MMSE) (Newkirk et al., 2004); attaining a score of 24 or more out of a possible 26 was required for inclusion in the study. A copy of the telephone MMSE is appended as Appendix D.

A minimum level of hand function was required to use the grip force equipment. Volunteers therefore had to be able to grasp and release a minimum of one block in the Box and Block Test (Mathiowetz, Volland, Kashman, & Weber, 1985) to take part. Full details of the Box and Block Test are outlined below in section 3.6.1 below.

A pragmatic assessment of visual acuity was applied. Volunteers had to be able to read the participant information sheet with or without corrective eyewear in order to be included. The final requirements for inclusion were that volunteers had to be willing to attend AUT University on four occasions for testing and consent to take part in the study.

3.5.2 Exclusion criteria.

Exclusion criteria were applied to limit any potential risk of harm to participants, and removed confounding factors of arm function. Volunteers with known contraindications to TMS were excluded from taking part in the assessment of cortical

excitability. This excluded any person with: a pacemaker, intracardiac lines, artificial heart valves containing conductive material, cranio-facial reconstruction or metal implants in the skull, face, or jaw (not including tooth fillings). People with precautions to receiving TMS were excluded; this included having a history of epilepsy or seizure, concussion within the previous 6 months, skull fracture or known skull defects, taking medication that lowered seizure threshold and/or a history of severe or recurrent headaches (Wassermann, 1998). Volunteers with a pacemaker were excluded on the basis that NMES was contraindicated. A copy of the TMS contraindications and precautions questionnaire is appended (see Appendix E).

Volunteers were excluded from the study if they had co-morbidities affecting upper limb function on the side most affected by the stroke. Volunteers were excluded from the assessment of cortical excitability if a motor evoked potential (MEP) could not be elicited in the target muscles. Any volunteer whose cortical excitability could not be assessed by reason of having contraindications or precautions to TMS, or because MEPs could not be elicited, was invited to take part in the grip control limb of the study (so long as NMES was not contraindicated).

3.6 Study procedure

3.6.1 Baseline measures.

During the first testing session participants were screened for contraindications or precautions to TMS and NMES and provided written informed consent to participating in the study. Figure 3.1 below provides a flow chart of the study

procedure. Details of the intervention, and pre- and post-intervention testing for TMS and grip control, will be covered in detail in sections 3.7.3, 3.7.4 and 3.7.5.

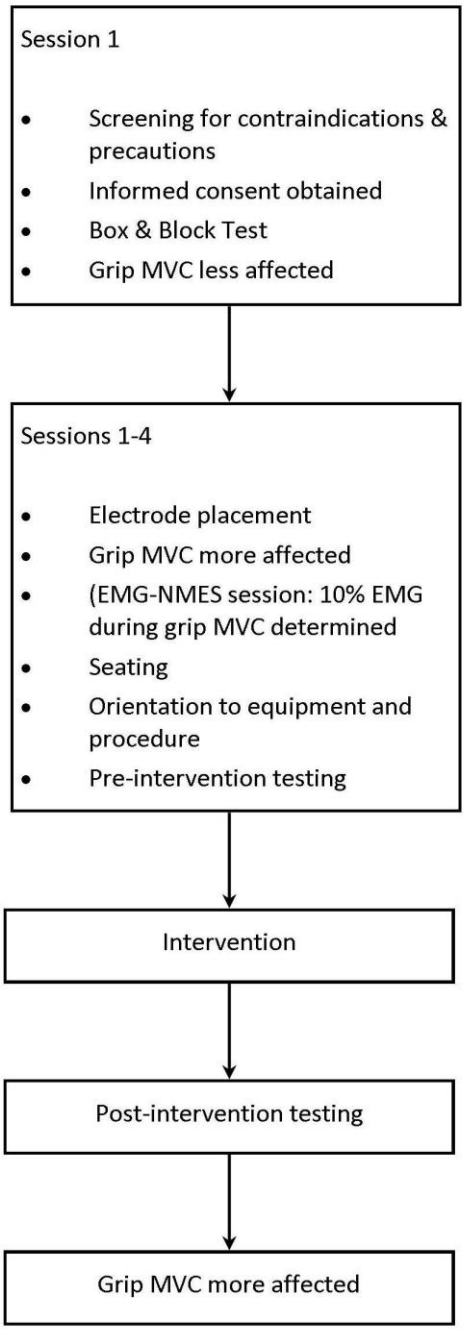


Figure 3.1. Flow chart of study procedure.

Note: grip MVC = maximal voluntary contraction (grip), EMG-NMES = EMG-triggered neuromuscular electrical stimulation, EMG = electromyography

Edinburgh Handedness Inventory

The Edinburgh Handedness Inventory was completed to determine each participant's hand dominance prior to stroke (Oldfield, 1971).

Box and Block Test

The Box and Block Test (Mathiowetz, 1985) was used to determine whether a volunteer could be included in the study as a participant and gave an indication of the functional ability of each participant in comparison with other study groups (Bhatt et al., 2007; Kimberley et al., 2004). The Box and Block Test has high test-retest reliability (Desrosiers, Bravo, Hebert, Dutil, & Mercier, 1994). The test has validity as a measure of dextrous hand function, confirmed by high correlations with upper limb and functional performance measures in older adults (Desrosiers et al., 1994). Adult normative scores for this test are available for comparison (Mathiowetz et al., 1985).

The Box and Block Test was performed using a custom made set constructed as specified by the authors of the test. To perform this test the participant picked up a small wooden cube (2.5cm square) from one side of a divided box and released the cube on the other side of the box. The score was determined by the number of cubes successfully transported one by one in a 60 second period, timed by the researcher with a stop watch. Each participant performed three repetitions with the affected hand and two with the less affected hand. The raw scores and average score obtained with each hand were recorded.

Maximal Grip Strength

At the first assessment, each participant's grip maximal voluntary contraction (MVC) for the more affected and less affected hand was obtained using a hand grip

dynamometer (Jamar™, Clifton, NJ). Using the Jamar to obtain grip MVC has been found to be reliable in community dwelling older adults (Schaubert & Bohannon, 2005), in healthy women, and in women with hand impairments (Nitschke, McMeeken, Burry, & Matyas, 1999). Normative scores for older adults using this equipment are available (Bohannon, Peolsson, Massy-Westropp, Desrosiers, & Bear-Lehman, 2006; Crosby, Wehbe, & Mawr, 1994).

In order to obtain an indication of the degree of strength impairment in the affected hand, each participant repeated grip MVC three times with each hand (Mathiowetz, Weber, Volland, & Kashman, 1984) and the raw scores and average score obtained were recorded. At every subsequent testing session each participant's grip MVC for the more affected hand alone was assessed prior to performing the cortical excitability or grip force baseline assessments, and again on completion of the testing session; this gave an indication of muscle fatigue following the interventions.

3.7 Experimental set-up

Participants were seated in front of a computer screen with their more affected forearm supported in a purpose built arm rest (see Figure 3.2, Figure 3.3 and Figure 3.4 below). At the outset of each session the participant confirmed they were able to see the computer monitor clearly; the participant's distance from the computer monitor and monitor orientation were not otherwise standardised. For the assessment of grip force and for the intervention tasks, the participant's hand rested in a pronated position on a custom built split spherical handle attached to a six degree-of-freedom force and torque transducer (67M25A 100N6, JR3 Inc, Woodland, CA). The force transducer measured

of forces up to 200 N, with a resolution of < 0.1 N. The height of the handle was determined according to each participant's comfort.

Figure 3.2. Seat set up.

Note: This shows the modified chair participants were seated in for the assessments and interventions. The purpose built forearm support is replacing the right armrest in this picture.

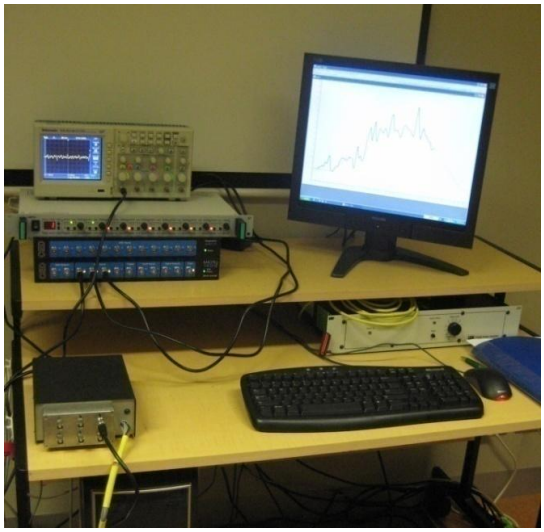


Figure 3.3. Computer set up.

Note: To the left of the computer monitor is the data acquisition board with the EMG amplifier and oscilloscope on top of it.

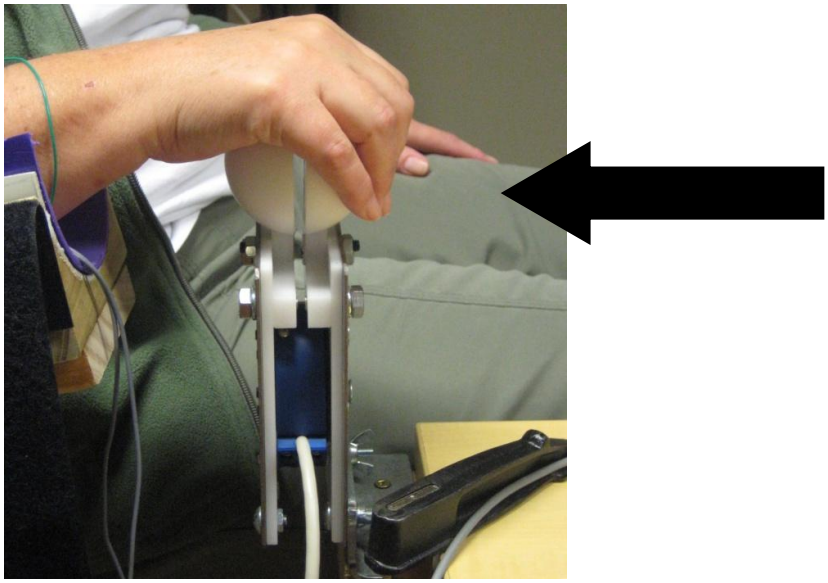


Figure 3.4. Force transducer and handle.

Note: The participant is resting their hand on the split spherical handle attached to the six degree-of-freedom force and torque transducer. The axis of force measurement is indicated by the arrow.

3.7.1 Electrode placement.

All electrodes were applied following standard skin preparation techniques of shaving to remove hair and cleansing with an alcohol wipe (Kendall Webcol™, Tyco, Mansfield, MA).

3.7.2 Surface electromyography.

EMG activity was collected in all experimental sessions from the superficial finger flexor (flexor digitorum superficialis, FDS) and extensor muscles (extensor digitorum). Nortrode 20™ Ag/Ag Cl 20 mm bi-polar self-adhesive surface electrodes (Myotronics Inc, Kent, WA) were applied over the finger flexor and extensor muscle bellies. The muscle bellies were located by palpation during active finger flexion and extension by the participant. Half a Nortrode 20™ electrode was applied to the lateral epicondyle of the elbow as a ground electrode.

EMG recordings were amplified (AMT-8 EMG Wire Telemetry System, Bortech Biomedical Ltd, Canada), filtered (10-1000 Hz), and sampled at 5000 Hz using an A/D converter (Micro1401 MkII, CED Ltd, Cambridge, UK). EMG data were stored for off-line analysis.

3.7.3 Cortical excitability assessment technique.

The excitability of neural pathways controlling hand and finger muscles was assessed before and after the grip training interventions using single and paired-pulse TMS. Stimuli were delivered by a Magstim 200^2 (Magstim Company, Dyfed, UK) with a figure-of-8 stimulation coil (70 mm diameter each coil) over the cortex contra-lateral to the more affected upper limb. The stimulating coil was placed over the participant's motor cortex with the handle orientated posteriorly and approximately 45° to the midline tangential to the scalp (Pascual-Leone, Cohen, Brasil-Neto, & Hallett, 1994).

The optimal site for stimulation was determined by systematically moving the coil and delivering supra-threshold stimuli until the site was located for eliciting the largest MEP in FDS in the more affected hand. Once identified, the coil position at this optimal site (hotspot) was marked by permanent marker on the participant's scalp. The hotspot was used as the stimulation site for the remainder of the session. For each TMS test stimulus, 200 ms of EMG data were collected, with an additional 50 ms prior to each stimulus.

TMS stimulation occurred while the FDS was at rest as determined by visual inspection of the real time EMG trace for FDS via an oscilloscope (TDS2014B, Tektronix Inc, Beaverton, OR). The resting threshold (RTh) for activation of FDS for each participant was determined at the beginning of each TMS session. RTh was taken

to be the lowest TMS intensity sufficient to elicit an MEP response of at least 50 μV in the FDS muscle in at least four out of eight consecutive stimuli.

A block of 24 TMS test stimuli were delivered over the hotspot. Test stimuli were delivered every 6 seconds ±15 %. These 24 stimuli consisted of eight stimuli for each of three stimulus protocols; one single pulse and two paired pulse. The single pulse test stimulus was set at 130 % RTh. The paired-pulse stimuli delivered two stimuli; a test stimulus set at 130 % RTh preceded by a conditioning stimulus at 80 % RTh. The interstimulus intervals for the conditioning and test stimuli were set at 2.5 ms to elicit and assess intracortical inhibition and at 12 ms to elicit and assess intracortical facilitation (Kujirai et al., 1993; Nakamura, Kitagawa, Kawaguchi, & Tsuji, 1997; Ziemann, Rothwell, & Ridding, 1996). The order in which the stimuli were delivered was randomised within each block of 24.

Figure 3.5 shows an example EMG trace for non conditioned MEPs from FDS of one participant.

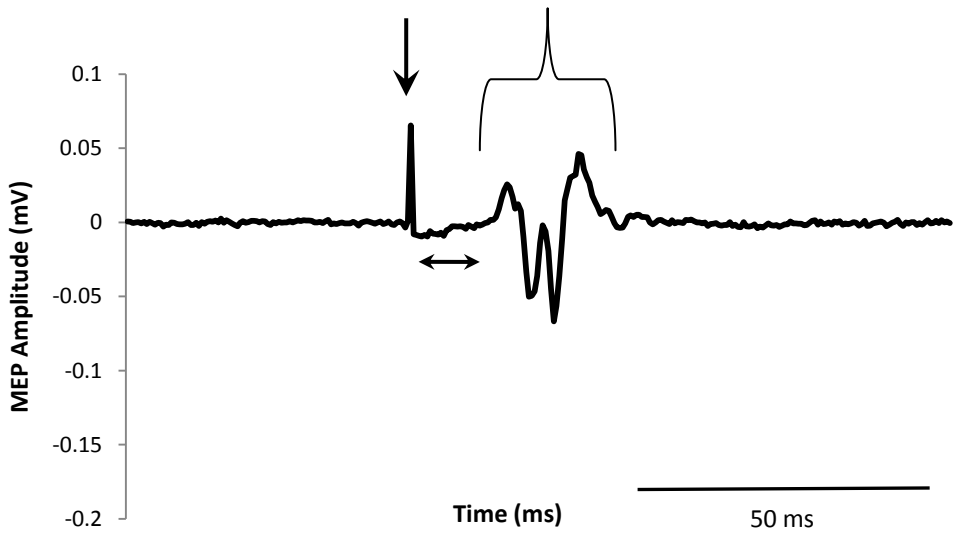
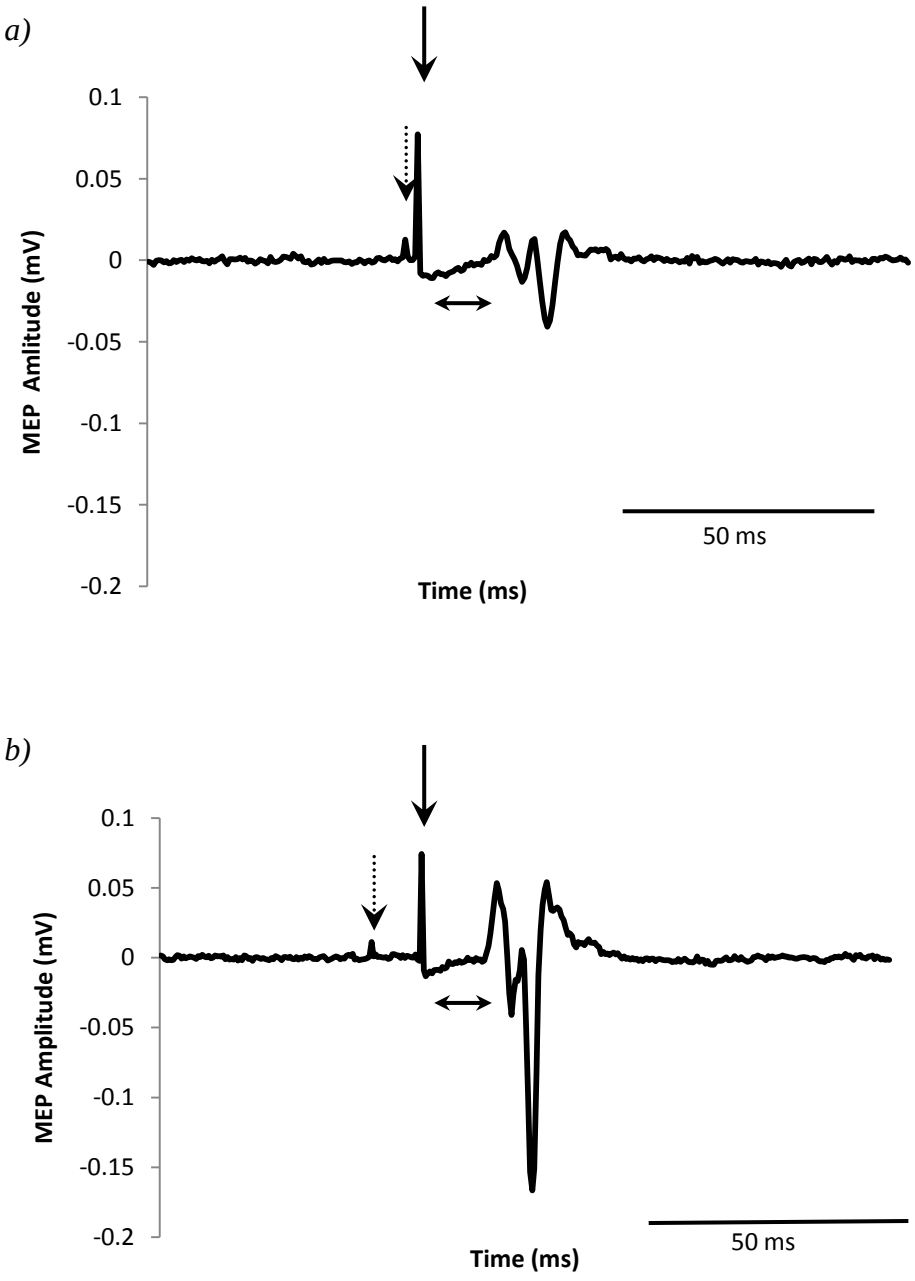


Figure 3.5. Non-conditioned MEP trace.

Note: MEP = motor evoked potential, mV = millivolts, ms = milliseconds. The MEP trace is an average of eight responses from the finger flexors following a non-conditioned TMS stimulus. The stimulus artefact is indicated by the vertical arrow. The MEP is indicated by the bracket. MEP latency, the period between stimulus and MEP onset, is indicated by the horizontal arrow.

Figure 3.6a shows the inhibitory and 3.6b the facilitatory effects on MEP amplitude of a conditioning stimulus preceding the test stimulus at 2.5 ms and 12 ms intervals respectively for the same participant.



Figures 3.6. a and b Conditioned MEP traces.

Note: a) The upper trace is an example MEP trace demonstrating the inhibitory effect on MEP amplitude of a conditioning stimulus preceding the test stimulus at a short (2.5 ms) interstimulus interval. b) The lower trace is an example MEP trace demonstrating the facilitatory effect on MEP amplitude of a conditioning stimulus preceding the test stimulus at a long (12 ms) interstimulus interval. In both figures, the conditioning stimulus (80% RTh) artefact is indicated by the dashed vertical arrow and the test stimulus (130% RTh) artefact by the solid vertical arrow. MEP latency, the period between stimulus and MEP onset, is indicated by the horizontal arrow. Both traces are an average of eight responses.

Participants received two baseline blocks of 24 stimuli with a five minute rest period between blocks. The two baseline measures were used to determine stability of cortical excitability prior to each intervention. Following the control or experimental intervention, participants received three further blocks of 24 TMS stimuli; immediately post-intervention, at five minutes post-intervention and at ten minutes post-intervention to assess the duration of any effects of the intervention on cortical excitability. A timeline of the TMS assessment points is set out in Figure 3.7 below.

Figure 3.7. Timeline of TMS assessment.

Note: Two baseline assessments of cortical excitability using TMS preceded the intervention. Post-intervention assessments were then repeated immediately after the intervention and at two further five minute intervals.

Similar TMS protocols have been found to have good reliability with respect to assessing MEP amplitude of the hand and forearm muscles of healthy participants (Lefebvre, Pepin, Louis, & Boucher, 2004; Malcolm et al., 2006; Nielsen, 1996). In participants with chronic stroke, variability in results for MEP amplitude of wrist and finger extensors is high between trials (Butler, Kahn, Wolf, & Weiss, 2005; McDonnell, Ridding, & Miles, 2004). These studies differ from the present study in that single pulse TMS techniques alone were used and the muscles group of interest were the wrist and finger extensors. However, these results indicate that evidence in support of the study

hypotheses (with respect to the effects of the interventions on cortical excitability) will only be provided if there are large changes in MEP amplitude post-intervention.

3.7.4 Grip control assessment technique.

Grip control was measured during two force tracking tasks performed by participants in separate sessions to the assessments of cortical excitability. The tracking tasks required participants to accurately adjust their voluntary grip force on the handle in response to visual feedback. Participants were required to modulate the amount of force they applied in order to match as closely as possible a target trace displayed on the computer monitor. Increasing grip force on the handle caused the participant's force trace represented on the computer display to ascend, and reducing grip force on the handle caused the force trace to descend. Participants were directed to adjust the amount of force by increasing or reducing the pressure applied by their fingers. Grip forces were measured in a single axis as shown in Figure 3.4 above.

At baseline (prior to the intervention), participants performed eight repetitions of each of two tracking tasks. The traces were generated and displayed using Spike2 software, version 6.08 (CED Ltd, Cambridge, UK). Participants received verbal feedback on task performance during the first three repetitions of each tracking task. The subsequent five repetitions were performed without verbal feedback, and these five trials were used as the pre-intervention test trials. The target trace remained on the screen throughout each tracking task. The first tracking task was a ramp task with maximum force target set at 8.5 N; requiring increase of force from 0 N to 8.5 N over 10 seconds, then holding the force trace at 8.5 N for 10 seconds before the target line descended to 0 N over 10 seconds. The total time for the ramp task was 30 seconds. Figure 3.8 shows an example of the ramp target. The ramp task required the participant

to be able to increase grip force and hold it stable over an extended period, accordingly this task provides an assessment of static grip control and endurance (Kurillo et al., 2004). The second tracking task was a sine wave with five waves oscillating between 2.5 N and 8.5 N over a 35 second period. The sine wave target was randomly generated; participants traced one sine wave form pre-intervention and a different sine wave form during the post-intervention assessment. Figure 3.9 shows an example of a randomly generated sine wave target. Each tracking task was preceded by a five second lead-in period. Grip control requirements of the sine wave task differ from the ramp task in that it requires rapid alternating increases and decreases of grip force to perform with accuracy (Kurillo et al., 2004). Similar tasks have been used previously to assess grip control (Kriz et al., 1995; Kurillo, Goljar, & Bajd, 2005a; Kurillo, Gregoric et al., 2005; Kurillo et al., 2004).

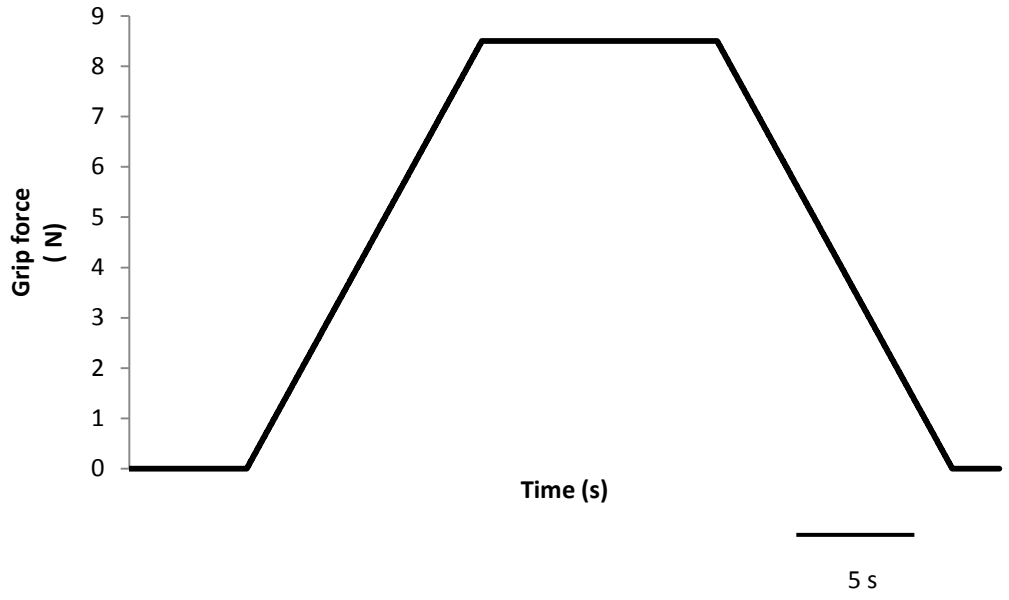


Figure 3.8. Ramp task target

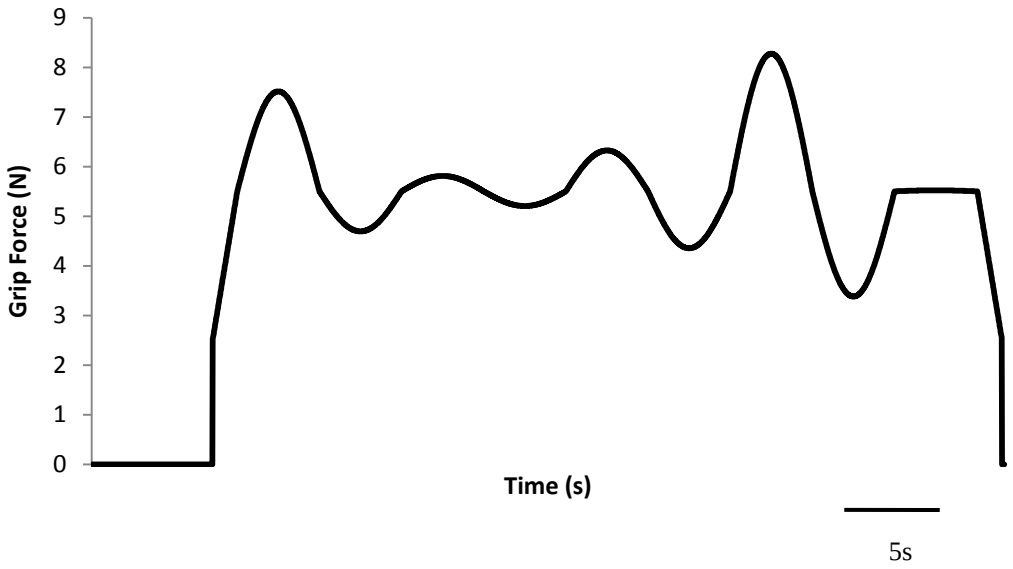


Figure 3.9. Sine wave task target

Following the control or experimental intervention, the participant performed five repetitions of each of the ramp and random sine wave tracking tasks. Figure 3.10 below shows this schematically. Prompting was not provided during the post-intervention repetitions of the tasks.

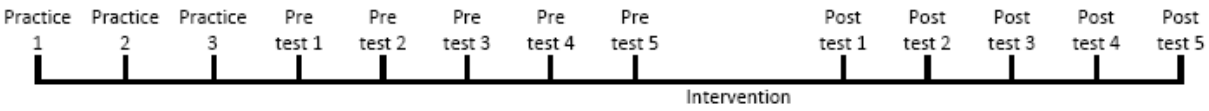


Figure 3.10. Timeline of grip force assessment.

Note: Three practice trials preceded the five pre-intervention test trials which were used in data analysis. At pre-intervention the participant performed eight repetitions of the ramp tracking task followed by eight repetitions of the random sine wave task. Following the intervention, the participant performed five repetitions of the ramp tracking task, followed by five repetitions of the random sine wave tracking task.

The maximum and minimum values for the force targets were determined *a priori*. Prior to the study, grip MVC was tested in a cohort of 7 people (4 men, 3

women) with stroke who were not enrolled in the study. MVC in the more affected hand ranged from 25 – 100 N in this group (*M* = 46.4 N, *SD* = 24.4 N). The minimum force target level during the sine wave task of 2.5 N was selected as consistent with 10 % of the lowest MVC. The maximum force target level for both the sine wave and ramp targets of 8.5 N represented approximately 30% of the lowest MVC recorded in the pre-study assessment of MVC and is the amount of force required to lift the force transducer and handle.

EMG data were collected simultaneously with force data during the grip control tasks. EMG signals were amplified and bandpass filtered (10-1000 Hz). Signals were sampled at 1000 Hz using a MacLab A/D (ADInstruments, Castle Hill, NSW) acquisition system.

3.7.5 Experimental and control interventions.

Both the experimental and control interventions used the same multi-digit grip force training task. The experimental intervention differed in employing EMG-NMES during the task. Using the split spherical handle attached to the force and torque transducer, participants were instructed to match a horizontal line displayed on the computer monitor in response to an auditory cue, and then relax their grip when cued to rest. Participants were directed to adjust the amount of force by increasing or reducing the pressure applied by their fingers. The horizontal target was set at 8.5 N. Each grip or 'work' phase was for six seconds, followed by a six second rest period. Participants performed two sets of 30 repetitions with a two minute rest break in between sets, comprising a total of 12 minutes of exercise. Figure 3.11 presents an excerpt of an example force trace from the training task.

The NMES unit (MyoTrac Infiniti^{TM}, Biomedical Instruments Inc, Warren MI) provided an auditory cue to grip and to release the sphere. Due to the fixed setup of the NMES unit, the cues to commence and cease grip during the training task differed for the control and exercise protocols. During the control intervention the cue to grip provided by the NMES unit was given by single beeps (1 per second for 6 seconds) and the rest period indicated by silence. During the experimental intervention the cue to grip was given by the NMES unit stating the word 'work' followed by single beeps (1 per second for 6 seconds) and the start of each rest period was cued by the NMES unit stating the word 'rest' followed by silence. Two participants had difficulty hearing the beeps during the control intervention; the researcher gave audible prompts of 'work' and 'rest' during those sessions.

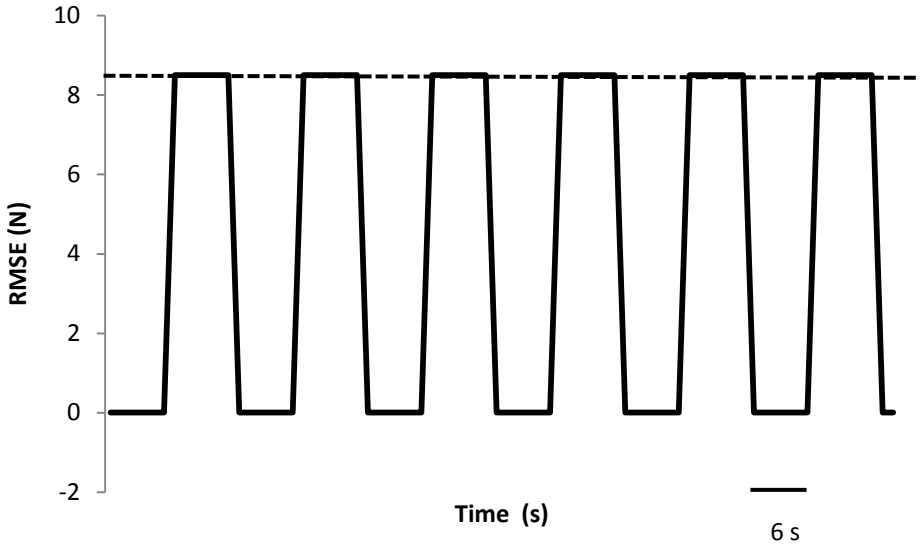


Figure 3.11. Example force trace for training task.

Note: The dashed horizontal line represents the target force level (8.5 N) the participant was required to match during the 'work' periods of the training task. The solid line represents the force produced by a participant in response to the cues to 'work' and 'rest'. This example trace shows six repetitions of 'work' and 'rest' phases, and is an excerpt of the total training task of 2 sets of 30 repetitions.

The rationale for this exercise prescription is to provide a short period of massed practice of a task to elicit motor learning while minimising the risk of fatigue. Short term increases in cortical excitability have been evoked in healthy participants following similar duration protocols using active movement, peripheral stimulation or EMG-NMES as the training stimulus (Classen et al., 1998; Hamdy, Rothwell, Aziz, Singh, & Thompson, 1998; Taylor et al., 2008).

3.7.6 EMG-NMES.

Electrode placement

For the exercise intervention sessions two 5 cm x 5 cm self adhesive Pals Platinum neurostimulation electrodes (Axelgaard, Fallbrook, CA) were applied over the motor points of FDS, each either side of the FDS EMG electrode. Half a Nortrode 20^{TM} electrode was applied to the medial epicondyle of the elbow as a ground electrode.

NMES parameters

The NMES parameters were set at the widest pulse width (400 µs) and highest frequency (100 Hz) permitted by the NMES unit as this protocol has been suggested to activate fatigue resistant fibres in preference to fast fatigable fibres (Baldwin et al, 2006; Dean et al, 2007, Panizza, 1992). The threshold of EMG activity for triggering the NMES stimulation was manually set prior to each intervention session. The maximal muscle activity for FDS was recorded during grip MVC using the digital output setting on the NMES unit. The EMG threshold to trigger NMES activation was set at 10% of the participant's maximum muscle activity during grip MVC.

NMES intensity was set at the maximum intensity tolerated by the participant once a visible contraction of the target muscle was obtained, as identified by finger

flexion in the relaxed FDS. This intensity was recorded and used as the NMES intensity for both sets of the EMG-NMES intervention within that session. NMES stimulation was triggered during the training task at the point the participant voluntarily activated FDS above the EMG threshold; NMES provided no stimulation during the six second rest period.

3.7.7 Post-intervention measures.

Following the final post-intervention assessment of cortical excitability and grip control, each participant performed three repetitions of grip MVC with the more affected hand. This was to provide an indirect measure of muscle fatigue following each intervention. Raw and average grip MVC results were recorded in newtons.

4 Data Processing and Analysis

4.1 Data processing

Written data were stored in a locked cabinet in the researcher's office. Computer data was stored on the laboratory computer; a back up copy was kept on a portable data device and stored with the written data. Confidentiality of all participant information and results was ensured by identifying each participant's demographic details and results by a numerical unique identifier. Only the researcher had access to the database which matched each unique identifier with the corresponding participant.

All statistical data analysis was performed using SPSS statistical software (SPSS 15.0 for Windows, SPSS Inc., Chicago, USA). Data entered in SPSS were checked against the raw data to ensure that data entry was accurate. Raw data were again reviewed for accuracy for any outlying values identified subsequent to statistical analysis. No data entry errors were identified.

4.2 Data analysis

4.2.1 Demographics and baseline data.

The range, mean and standard deviations were identified for continuous baseline and demographic data of age, time since stroke and grip MVC. Sample characteristics of gender, MMSE score, functional dexterity as measured by the Box and Block Test, handedness and concordance of stroke affected side to dominant hand were analysed using descriptive statistics appropriate to nominal and ordinal data.

4.2.2 Cortical excitability.

Data analysis of cortical excitability measures was performed using Signal software (CED, Cambridge, UK). Corticomotor and intracortical excitability were assessed for FDS at each time point (baseline 1, baseline 2, post intervention, post intervention + 5 minutes, post intervention + 10 minutes) using single pulse (non-conditioned) and paired-pulse (intracortical inhibition, intracortical facilitation) TMS.

MEP Processing

Muscle activation will alter measures of cortical excitability (Ridding, Taylor, & Rothwell, 1995); any recordings showing background muscle activation were therefore removed prior to further processing. MEP data were analysed by measuring MEP peak-to-peak amplitude for each MEP and then averaging the results, and by averaging the MEP amplitude for each inter-stimulus interval then measuring the result for each time point. The latter approach is commonly adopted (Benwell et al., 2006; Lewis, Byblow, & Carson, 2001). Raw MEP data were used for this analysis. A scatter plot of the results (see Figure 4.1) with line of best fit shows the linear relationship between the two measurement approaches following analysis of two participants' results from four TMS sessions.

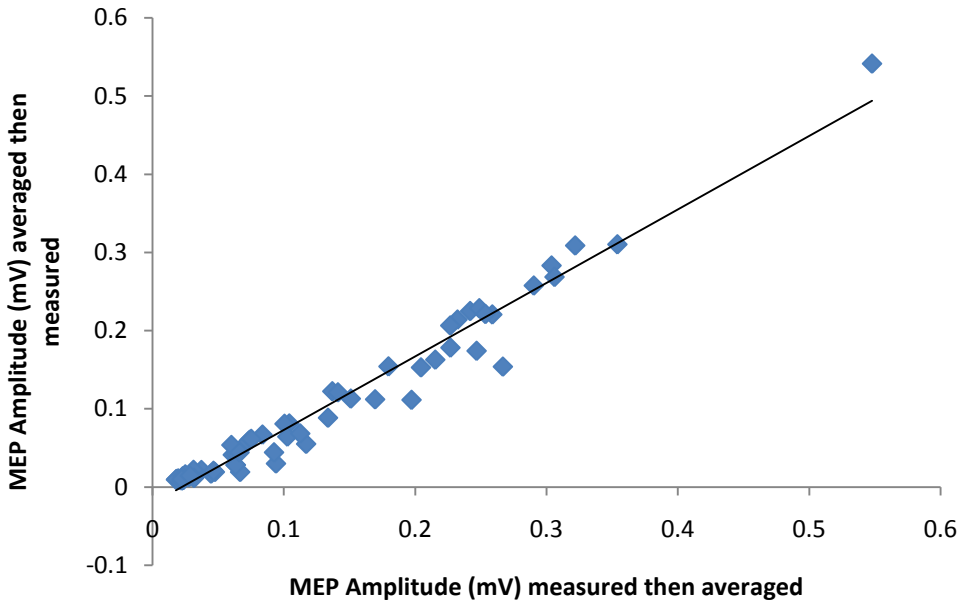


Figure 4.1. Relationship between MEP Amplitude measurement techniques.
Note: MEP = motor evoked potential, mV = millivolts

This linear relationship between the two methods of MEP amplitude measurement was confirmed by correlation analysis ($r = 0.98$, $p < .01$). As the results from each measurement technique were equivalent, MEP results were determined for each time point by averaging the eight MEPs for each inter-stimulus interval and subsequently measuring the variables of interest from the averaged response.

MEP Measurements

For each averaged MEP the following were recorded: root mean square amplitude of background EMG during a 30 ms pre-stimulus window (background RMS), peak-to-peak MEP amplitude and latency between stimulus and MEP onset. Averaged rectified MEP data were used for measuring background RMS. Peak-to-peak MEP amplitude was measured from the averaged raw MEP data and determined by the maximum peak amplitude in a 40 ms window following MEP onset. Non-conditioned

MEP amplitude at baseline 2 and each subsequent time point was normalised to baseline 1 non-conditioned MEP amplitude. To determine measures of intracortical inhibition and intracortical facilitation, conditioned MEP amplitudes were expressed relative to the non-conditioned MEP amplitude (Kujirai et al., 1993). Values less than 1 indicate MEP inhibition and greater than 1 indicate MEP facilitation. MEP latency was defined as the first point following the stimulus artefact that the EMG signal exceeded the background RMS by 3 standard deviations. This was confirmed for all responses by visual inspection.

4.2.3 Grip control.

Performance during the tracking tasks was quantified by calculating the root mean square error (RMSE) between the target force trace and the actual force trace generated by the subject (Kriz et al., 1995). This can be expressed as:

$$\text{RMSE} = \sqrt{\frac{\sum (A_f - T_f)^2}{N}}$$

where A_f is the actual force, T_f is the target force and N is the number of data points. The RMSE provides a measure of performance deviation, with lower values reflecting more accurate performance. The ramp and sine wave tasks were sectioned into shorter time periods for analysis of RMSE. This enabled assessment of the different phases of each task to be evaluated separately, and omitted any increase in variability of performance associated with the beginning and end of each task. A similar measurement

approach has been taken in previous force tracking studies (Kriz et al., 1995; Kurillo, Gregoric et al., 2005; Kurillo et al., 2004). RMSE was calculated for three time periods during the ramp task, and one for the sine wave task. For the ramp task, the middle 8 seconds of each phase (ascent, hold and descent) were analysed. For the 30 second sine wave task, RMSE was calculated for the middle 28 seconds of the task.

4.2.4 Statistical analyses.

Mean and standard error values were plotted on line graphs and any outliers confirmed as correct by reference back to the raw data. All outliers were included in the analyses. Significance levels for all analyses were set at $p \leq .05$. Kolmogorov-Smirnov tests confirmed that baseline variables (age, time since stroke and Box and Block Test score), grip MVC, MEP amplitude, and grip control RMSE were all normally distributed. Parametric tests were therefore applied. Dependent variables for the assessment of cortical excitability were background RMS, MEP amplitude, intracortical inhibition, intracortical facilitation and MEP latency. Independent variables were treatment group (EMG-NMES, voluntary activation); referred to in the analyses as 'group', and time (pre-intervention, post-intervention, post-intervention + 5 minutes, post-intervention + 10 minutes). The dependent variable for the assessment of grip control was RMSE. RMSE was calculated for each of the three phases of the ramp task (ramp ascent, ramp hold, ramp descent) and for the sine wave task. The independent variables for grip control were treatment group (EMG-NMES, voluntary activation); referred to in the analyses as 'group', and time (pre-intervention, post-intervention).

Cortical excitability

Stability of TMS measures prior to the interventions was determined by paired sample t-tests of: background RMS prior to the non-conditioned stimulus, MEP amplitude, and non-conditioned MEP latency at baseline 1 compared to baseline 2. It was determined *a priori* that if dependent TMS variables were stable, baseline 2 values would be used in all subsequent analyses as the pre-intervention measure. To assess the effect of the interventions, dependent variables were analysed using a two-way repeated measures ANOVA with within-subject factors of treatment and time. Sphericity of data was determined by applying Mauchly's test in respect of the main effect of time and interaction effect of intervention x time. Where the assumption of sphericity was violated, and Epsilon < 1, Greenhouse-Geisser corrections were used. Significant main effects of time were investigated by comparing the three post-intervention time periods (post-intervention, post-intervention + 5 minutes, post-intervention + 10 minutes) to baseline 2.

Grip control

RMSE results for the first eight repetitions of the grip control task were plotted against time in order to identify any training effect. Variability of RMSE of these eight repetitions was identified by plotting the standard error of the mean. To identify any intervention effect on RMSE, the best performance (lowest RMSE) from each of the five pre- and post-intervention traces for each tracking task was analysed (Kurillo et al., 2004).

The effect of the interventions on RMSE was analysed using a two-way repeated measures ANOVA with within-subject factors of treatment (EMG-triggered NMES, voluntary activation) and time (pre-intervention, post-intervention).

Grip MVC

Any change in grip MVC over time was calculated to provide an indirect measure of muscle fatigue. The effect of intervention on grip MVC was calculated using a two-way repeated measures ANOVA with within-subject factors of treatment (EMG-triggered NMES, voluntary activation) and time (pre-intervention, post-intervention). Grip MVC was analysed in two parts determined according to outcome measure due to the different numbers of participants taking part in the cortical excitability and grip control assessments.

5 Results

5.1 Introduction

The results of the study are presented in this chapter. The purpose of the study was to identify whether any immediate changes in cortical excitability and/or grip control would occur in a sample of participants with stroke, after a short intervention of either EMG-NMES or voluntary activation training. This chapter first sets out the results of recruitment, retention and data screening. Following this, the sample characteristics (including demographic, stroke characteristics and baseline physical functioning) are identified. This chapter concludes with analysis of the effect of the interventions on cortical excitability and grip control.

5.2 Recruitment and retention

Nineteen people volunteered to take part in the study, of these 15 met the inclusion criteria. Five of the people included either could not participate or declined to participate in the assessment of cortical excitability using TMS. These five people consented to take part in the assessment of grip control. Accordingly, grip control was assessed in 15 participants and measures of cortical excitability were assessed in ten participants. No participants dropped out of the study; however, one participant (P14) was unable to maintain a resting state in FDS for the final time period during both sessions assessing cortical excitability. The data from this participant for post exercise + 10 minutes was therefore omitted, and results for this time point calculated from nine

participants. Data collection took place from September 2008 to April 2009. The flow diagram set out in Figure 5.1 below provides an outline of the recruitment process.

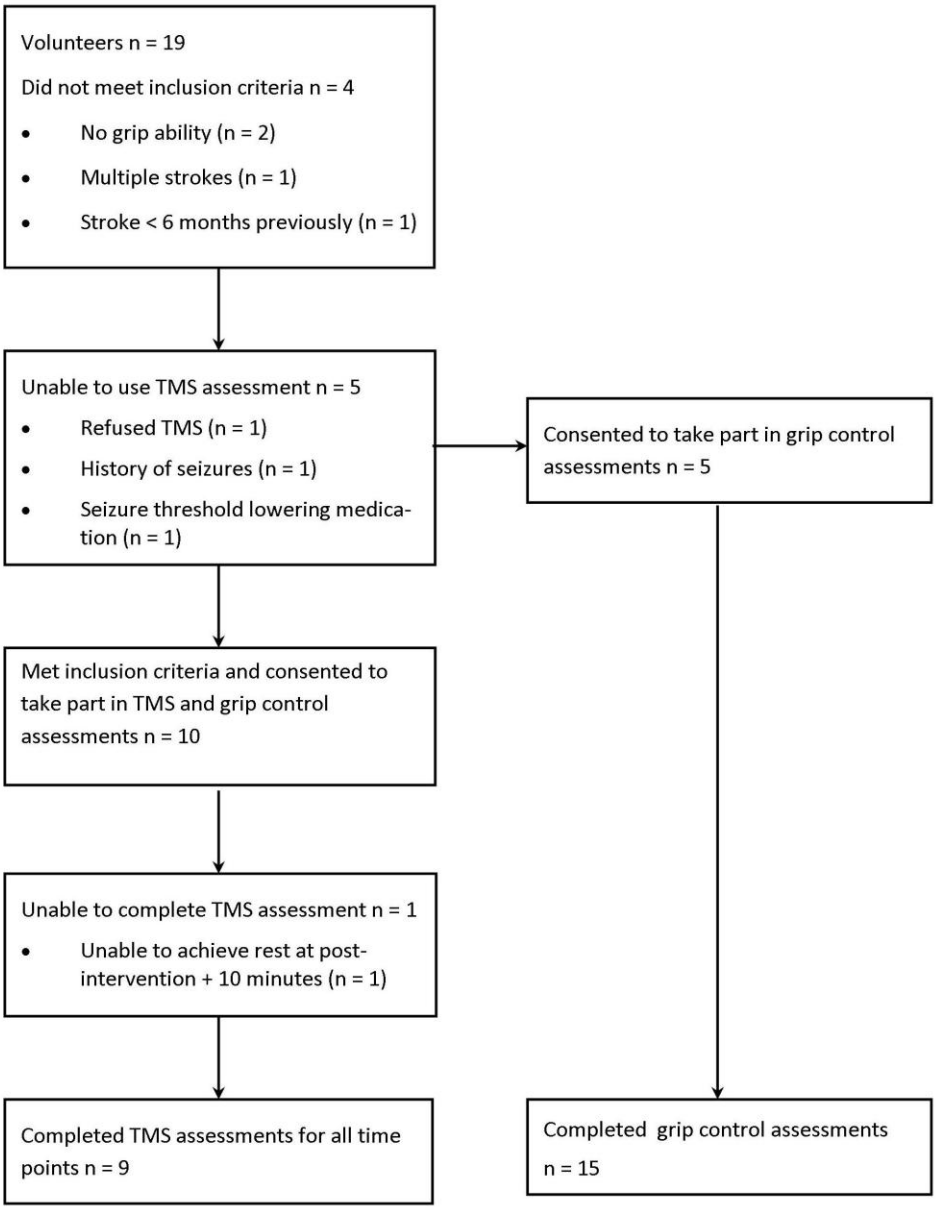


Figure 5.1. Flow diagram of participant recruitment.

Note: TMS = transcranial magnetic stimulation

5.3 Data screening

Monitoring of EMG during data collection indicated that most participants found it difficult to maintain wrist and finger extensor muscles in a resting state while cortical excitability was being assessed. On review of the data, only one participant had sufficiently quiet extensor EMG throughout the TMS assessment to warrant retention of this data. Accordingly, MEP data for FDS only has been included in the statistical analyses of cortical excitability.

5.4 Sample characteristics

Demographic and clinical data for included participants are presented in Table 5.1 including: age, gender, time since stroke, Telephone MMSE score, side of hemiplegia and concordance. Concordance of stroke is indicated by whether or not the more affected limb is the participant's dominant limb, as shown by the Edinburgh Handedness Inventory score. The age of participants ranged between 52 and 84 years (M =70, SD = 9 years). Time since stroke ranged between 9 and 196 months (M = 54, SD = 50 months). Eleven out of the 15 participants were male, four were female. Eight participants had a left hemiplegia. Most participants' hemiplegia involved their non-dominant hand as shown by nine participants' hemiplegia being discordant with hand dominance. Due to restrictions imposed by the inclusion criteria, Telephone MMSE scores fell within a very small range (24 – 26 out of a maximum score of 26).

Table 5.1

Participants' demographic and stroke data

Participant	Gender	Age (years)	Time since stroke (months)	TMMSE (/26)	Hemiplegia	Concordance
P1	M	73	21	26	L	N
P2	M	71	16	24	L	N
P3	F	61	94	24	L	N
P4	M	69	104	24	R	Y
P5	M	61	24	24	R	N
P6	M	84	9	24	R	Y
P7	M	75	196	26	R	Y
P8	M	81	46	24	L	N
P9	F	60	41	24	R	Y
P10	M	72	88	24	R	N
P11	F	79	29	25	L	N
P12	M	79	14	24	L	N
P13	F	52	16	26	R	Y
P14	M	60	72	25	L	N
P15	M	76	34	24	L	Y
M		70	54			
SD		9	50			

Note. TMMSE = Telephone MMSE, M = mean, SD = standard deviation. Concordance = whether most affected hand was the participant's dominant hand as indicated by the Edinburgh Handedness Inventory score; Y = more affected hand is participant's dominant hand, N = more affected hand is participant's non-dominant hand.

5.5 Baseline physical function

Baseline physical function of the participants is set out in Table 5.2. This included the number of blocks transferred during the Box and Block Test and grip MVC. The participants had lower Box and Block Test scores for their more affected hand compared to their less affected hand and this difference was statistically significant ($t(14) = -5.154$, $p < .001$). The more affected hand was also weaker than the less affected hand; the difference in grip strength between hands was statistically significant ($t(14) = -2.838$, $p = .013$).

Table 5.2

Participants' physical function at baseline

Test	Mean		SD	Minimum	Maximum
B&B A	38	**	16	6	69
B&B L	61		13	39	90
MVC A	43.3	*	15.6	13.3	63.3
MVC L	59.7		16.3	28.3	94.0

Note. B&B A = Box & Block Test more affected hand, B&B L = Box & Block Test less affected hand, MVC A = maximum grip force more affected hand (newtons), MVC L = maximum grip force less affected hand (newtons), SD = standard deviation.
* $p \leq .05$ ** $p \leq .001$

5.6 Measures of cortical excitability

5.6.1 Introduction.

The results of the background RMS, MEP amplitudes for single (non-conditioned) and paired-pulse (intracortical inhibition, intracortical facilitation) states

and MEP latency, were normally distributed for each time point and each intervention. Parametric statistical analyses using two-way ANOVA were therefore applied to identify main effects of intervention and of time and interactions between interventions and time for each of these aspects of cortical excitability.

5.6.2 Stimulus intensity.

Mean RTh as a percentage of TMS stimulator output was 51% (*SD* = 11%) during the voluntary activation intervention, and 52% (SD = 13%) during the EMG-NMES intervention. Mean conditioning stimulus at 80% RTh was 41% (*SD* = 9%) during the voluntary activation intervention, and 42% (*SD* = 11%) during the EMG-NMES intervention. Mean test stimulus at 130% RTh was 66% (*SD* = 15%) during the voluntary activation intervention, and 67% (*SD* = 16%) during the EMG-NMES intervention. There was no significant difference in RTh ($t(9) = -.747$, $p = .483$), conditioning stimulus ($t(9) = -.694$, $p = .505$), or test stimulus intensity ($t(9) = -.196$, $p = .849$) between the two sessions.

5.6.3 Background EMG RMS.

Background RMS is the root mean square of the amplitude of background EMG during a 30 ms window prior to the TMS stimuli. The level of muscle activity prior to this stimulus will influence MEP amplitude (Rothwell et al., 1987). Accordingly, background RMS was measured to ensure equivalent motoneuron activity between interventions and time periods.

Prior to non-conditioned MEP

Paired t-tests showed no significant difference in background RMS prior to the non-conditioned test stimulus between baseline 1 and baseline 2 for the EMG-NMES intervention ($t(9) = 0.327$, $p = .751$) or the voluntary activation intervention ($t(9) = 0.949$, $p = .367$). Baseline 2 values have therefore been used as the pre-intervention data in the analyses of background RMS. Mauchly's test indicated that sphericity could be assumed for the main effect of time ($\chi^2(5) = 4.439$, $p = .492$) and interaction effect of intervention x time ($\chi^2(5) = 4.633$, $p = .466$) accordingly no correction to degrees of freedom was required. There was no significant main effect of intervention ($F(1, 8) = 4.673$, $p = .63$) or time ($F(3, 24) = 0.183$, $p = .907$) or interaction effect of intervention x time ($F(3, 24) = 0.151$ $p = .928$) on background RMS prior to the assessment of non-conditioned MEP amplitude.

Prior to conditioned MEP (2.5 ms interstimulus interval)

Mauchly's test indicated that sphericity could be assumed for the main effect of time ($\chi^2(5) = 1.716$, $p = .888$) and interaction effect of intervention x time ($\chi^2(5) = 6.786$, $p = .241$) accordingly no correction to degrees of freedom was required. There was a significant main effect of intervention on background RMS prior to the conditioned stimulus, ($F(1,8) = 5.790$, $p = .043$). Mean background RMS measured prior to the conditioned stimulus was higher ($M = 2.97$ µV, $SD = 0.90$ µV) prior to the EMG-NMES intervention than prior to the voluntary activation intervention ($M = 2.53$ µV, $SD = 0.15$ µV), see Figure 5.2. There was no significant main effect of time ($F(3, 24) = 2.047$, $p = .134$) or interaction effect of intervention x time ($F(3, 24) = 0.014$ $p = .998$) on background RMS prior to assessment of intracortical inhibition.

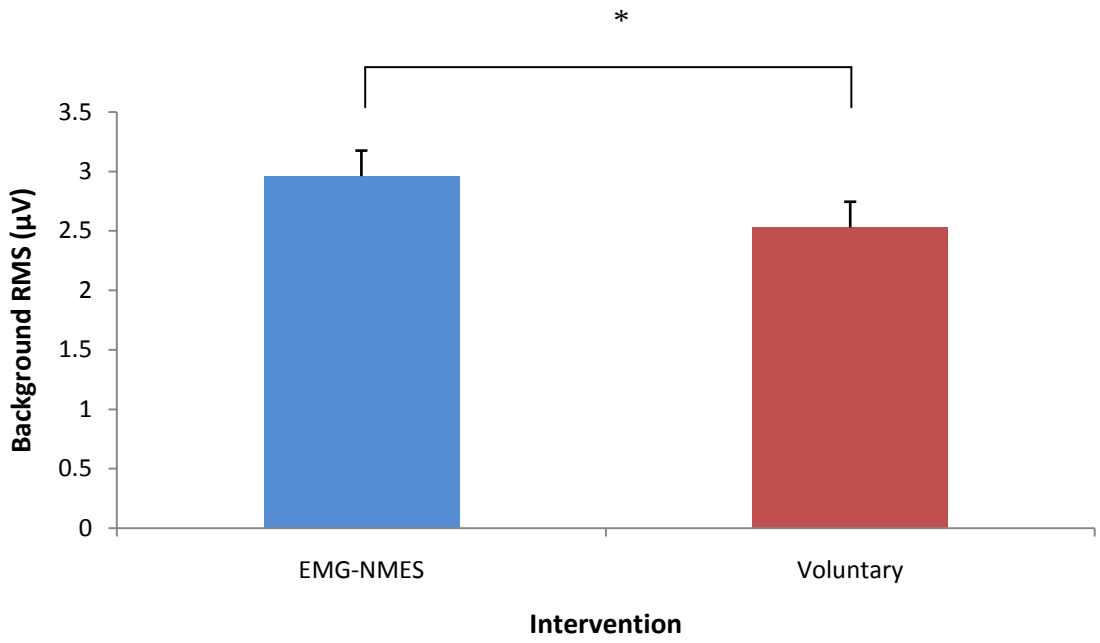


Figure 5.2. Background root mean square EMG amplitude prior to measurement of intracortical inhibition.

Note: Error bars indicate standard error of the mean. Background RMS = Background root mean square of electromyography amplitude, µV = microvolts, EMG-NMES = electromyography triggered neuromuscular electrical stimulation intervention, Voluntary = voluntary activation intervention.
** $p \leq .05$*

Prior to conditioned MEP (12 ms interstimulus interval)

Mauchly's test indicated that sphericity could be assumed for the main effect of time ($\chi^2(5) = 10.42$, $p = .067$) and interaction effect of intervention x time ($\chi^2(5) = 7.186$, $p = .211$) accordingly no correction to degrees of freedom was required. There was no significant main effect of intervention ($F(1, 8) = 2.910$, $p = .126$) or time ($F(3, 24) = 0.857$, $p = .477$) or interaction effect of intervention x time ($F(3, 24) = 0.060$ $p = .980$) on background RMS assessed prior to intracortical facilitation.

5.6.4 Normalised non-conditioned MEP amplitude.

Non-conditioned MEP amplitude was used as a measure of cortico-motor excitability. Paired t-tests showed no significant difference in non-conditioned MEP amplitude between baseline 1 and baseline 2 for the EMG-NMES intervention ($t(9) = -0.922$, $p = .381$) or for the voluntary activation intervention ($t(9) = 0.986$, $p = .350$). Baseline 2 values have therefore been used as the pre-intervention data in the analyses. Mean non-conditioned MEP amplitude at baseline 2 was 0.202 mV ($SD = 0.278$ mV) prior to the EMG-NMES intervention, and 0.199 mV ($SD = 0.206$ mV) prior to the voluntary activation intervention. Example non-conditioned MEP traces from one participant before and after the EMG-NMES intervention are presented in Figure 5.3.

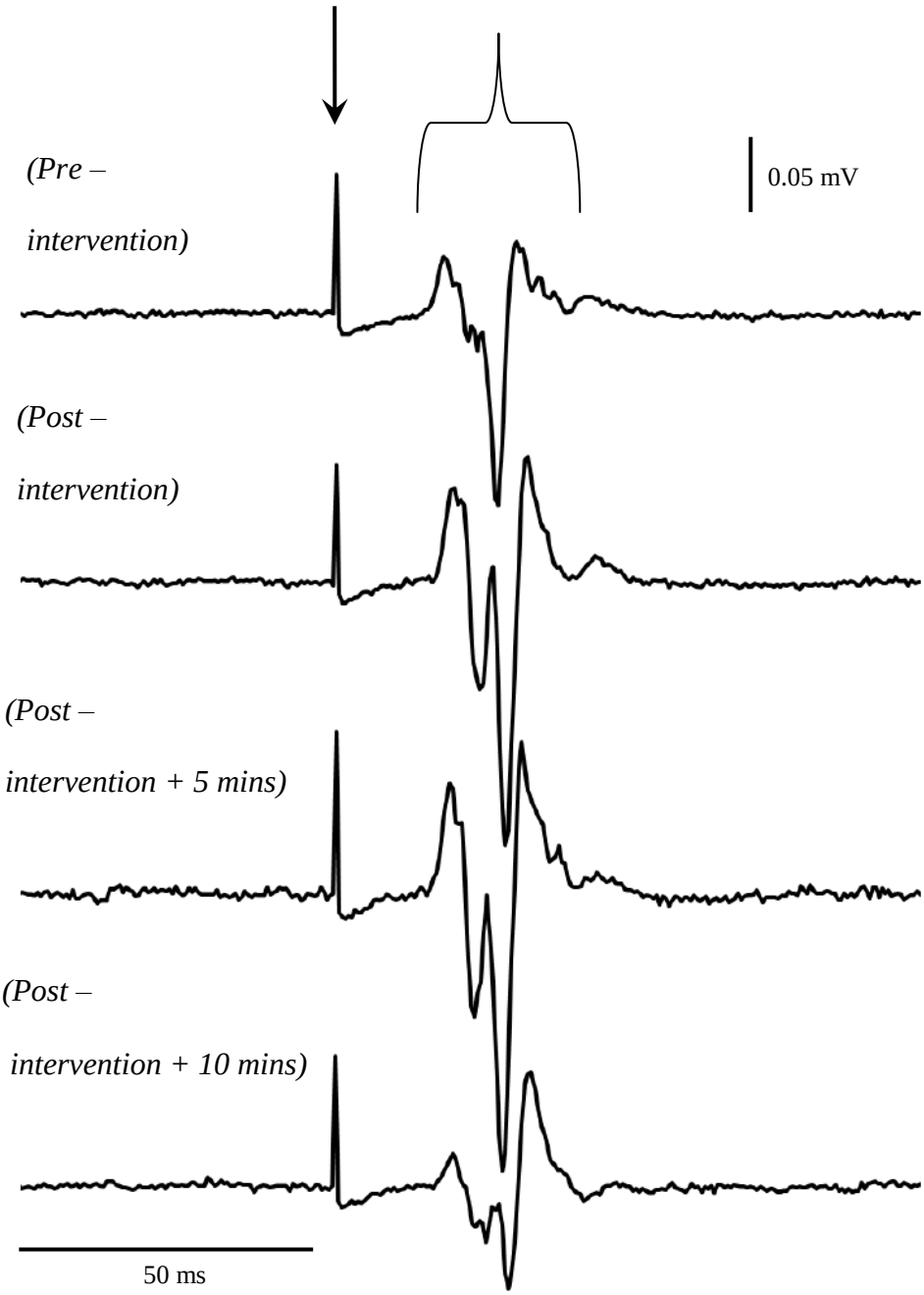


Figure 5.3. Example non-conditioned MEP traces over time from one participant.

Note: This figure shows non-conditioned MEP amplitude over time for one participant (P3), before and after the EMG-NMES intervention. Traces are an average of eight responses. The arrow indicates the stimulus artefact. The bracket indicates the MEP.

5.6.5 Group comparisons.

Mauchly's test indicated the assumption of sphericity had been violated for the main effect of time ($\chi^2(5) = 12.924$, $p = .026$) and for the interaction effect of intervention by time ($\chi^2(5) = 17.563$, $p = .004$). Accordingly, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.486$ for the main effect of time and $\varepsilon = 0.422$ for the interaction effect of intervention x time) (Field, 2005).

The group comparison results are displayed graphically in Figure 5.4. There was no significant main effect for intervention ($F(1, 8) = 0.23$, $p = .883$), or time ($F(1.49, 11.671) = 1.\ 032$, $p = .363$), or interaction effect of intervention x time ($F(1.265, 10.121) = 0.478$, $p = .549$) on normalised non-conditioned MEP amplitude. Accordingly, the hypotheses that both interventions would result in increased MEP amplitude post-intervention and that EMG-NMES would result in greater increases in cortical excitability at post-intervention compared to voluntary activation, are not supported by these results.

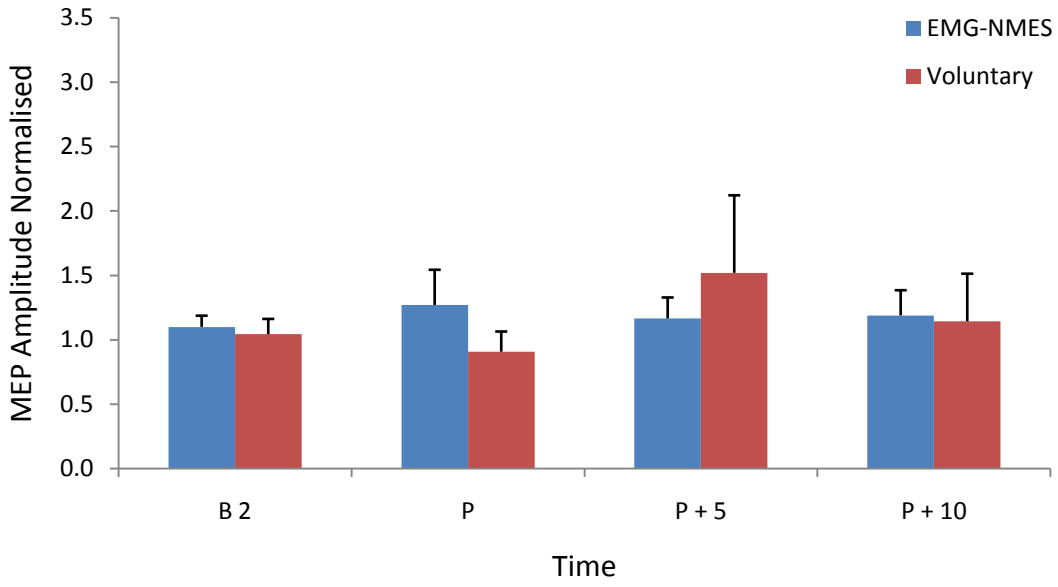


Figure 5.4. Group results for normalised non-conditioned MEP amplitude over time.

Note: Error bars show standard error of the mean. EMG-NMES = electromyography triggered neuromuscular electrical stimulation intervention, Voluntary = voluntary activation intervention, B 2 = baseline 2, P = post-intervention, P + 5 = post-intervention + 5 minutes, P + 10 = post-intervention + 10 minutes; MEP amplitude for baseline 2 and each subsequent time point was normalised to baseline 1.

5.6.6 Intracortical inhibition.

Intracortical inhibition was expressed at each time point as conditioned MEP amplitude (with a 2.5 ms interstimulus interval) relative to non-conditioned MEP amplitude at that time point. Paired t-tests showed no significant difference between the two interventions at baseline 2 ($t(9) = 1.94$, $p = .084$) for intracortical inhibition. Mean intracortical inhibition at baseline 2 was 0.578 ($SD = 0.375$) prior to the EMG-NMES intervention, and 0.345 ($SD = 0.217$) prior to the voluntary activation intervention. Example conditioned MEP traces (with a 2.5 ms interstimulus interval) from one participant before and after the EMG-NMES intervention are presented in Figure 5.5 below.

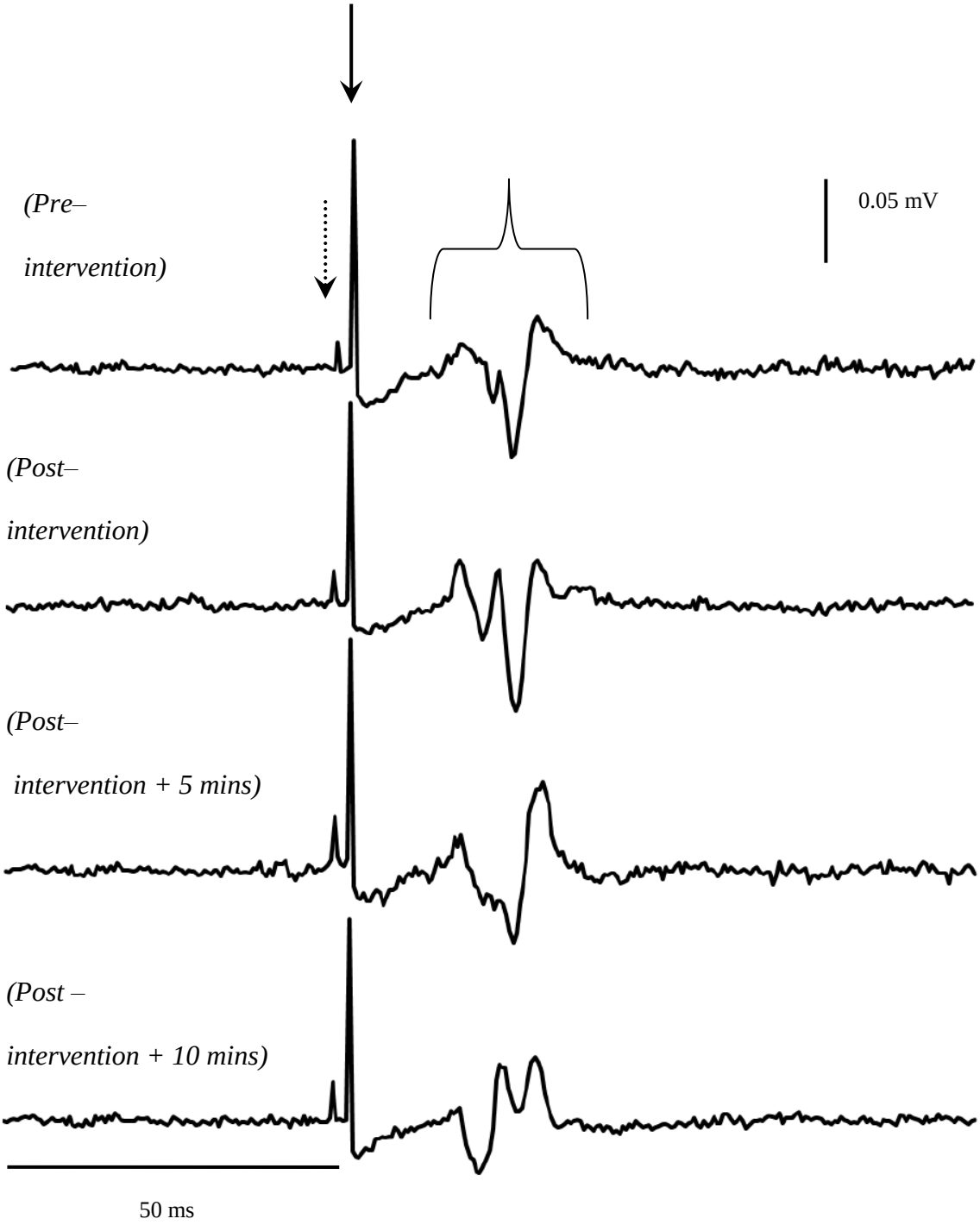


Figure 5.5. Example conditioned MEP traces (2.5 ms interstimulus interval) over time from one participant.

Note: This figure shows intracortical inhibition by conditioned MEP amplitude over time for one participant (P3), before and after the EMG-NMES intervention. The broken arrow indicates the conditioning stimulus (80 % resting threshold) for FDS 2.5 ms prior to the test stimulus (130 % resting threshold). The solid arrow indicates the stimulus artefact. The bracket indicates the MEP. Traces are an average of eight responses.

Group Comparisons

Mauchly's test indicated that sphericity could be assumed for the main effect of time ($\chi^2(5) = 6.565$, $p = .259$) and for the interaction effect of intervention x time ($\chi^2(5) = 4.634$, $p = .466$); accordingly, no correction to degrees of freedom was required. There was a significant interaction effect between the intervention used and the time point of assessment ($F(3, 24) = 3.414$, $p = .034$), indicating that the type of intervention had a different effect on intracortical inhibition across the four time periods, this result is presented graphically in Figure 5.6 below. There was no significant main effect of intervention ($F(1,8) = 0.010$, $p = .921$), or time ($F(3, 24) = 0.780$, $p = .517$) on intracortical inhibition.

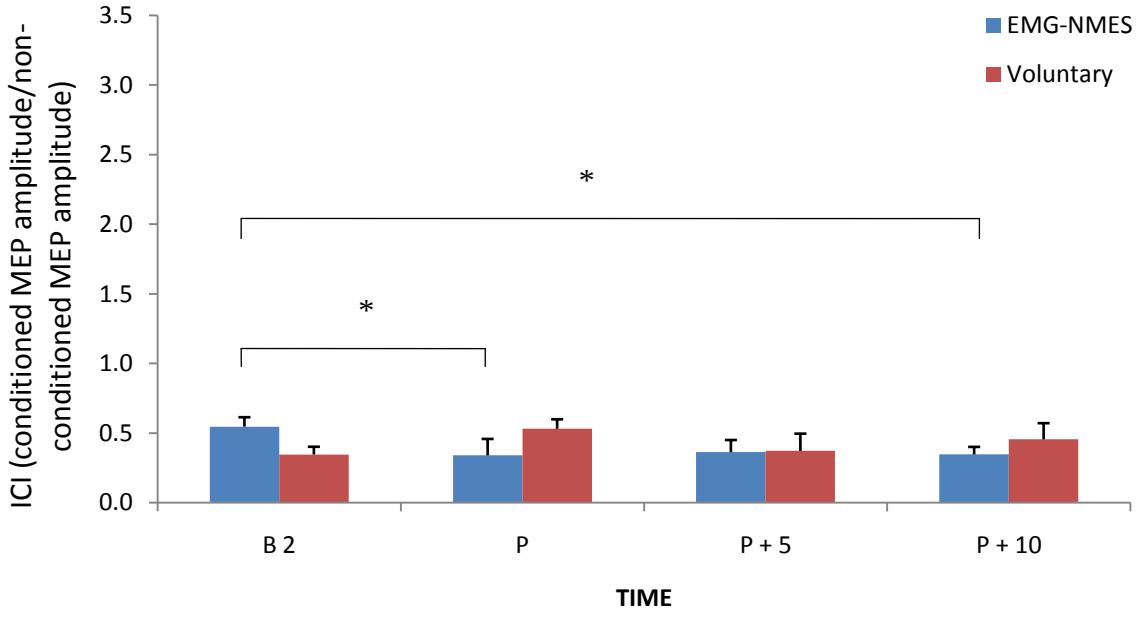


Figure 5.6. Group results for intracortical inhibition over time.

Note: Error bars indicate standard error of the mean. EMG-NMES = electromyography triggered neuromuscular electrical stimulation intervention, Voluntary = voluntary activation intervention, ICI = intracortical inhibition, MEP = motor evoked potential, B 2 = baseline 2, P = post-intervention, P + 5 = post-intervention + 5 minutes, P + 10 = post-intervention + 10 minutes. MEP amplitude for baseline 2 and each subsequent time point was normalised to baseline 1.
** $p \leq .05$ for EMG-NMES intervention compared to baseline 2*

In light of the interaction effect of intervention x time, post hoc tests were performed to analyse whether there was any significant difference in intracortical inhibition between each post-intervention assessment and baseline 2 for each intervention. Table 5.3 shows the significant increase in intracortical inhibition at post-intervention and post-intervention + 10 minutes compared to baseline 2 following the EMG-NMES intervention. There was no significant difference in intracortical inhibition at the time points following the voluntary activation intervention, compared to baseline 2.

Table 5.3

Paired t-tests for intracortical inhibition post-intervention compared to baseline 2

	EMG-NMES paired differences			
Time	M	SD	*t*	*p*
PI[a]	0.207	0.265	2.466	.036*
PI + 5[a]	0.183	0.282	2.057	.070
PI + 10[b]	0.232	0.284	2.450	.040*
	Voluntary activation paired differences			
PI[a]	-0.185	0.377	-1.549	.156
PI + 5[a]	-0.025	0.272	-0.294	.776
PI + 10[b]	-1.10	0.187	-1.760	.116

Note. a. *N* = 10, b. *N* = 9, M = mean, SD = standard deviation, t = computed value of t-test, *p* = probability, PI = post-intervention, PI + 5 = post-intervention + 5 minutes, PI + 10 = post-intervention + 10 minutes
* $p \leq .05$

As conditioned MEP amplitude reduced following EMG-NMES, this represents an increase in intracortical inhibition. Accordingly, the hypotheses that EMG-NMES would result in reduced intracortical inhibition at post-intervention, and reduced intracortical inhibition compared to voluntary activation, are not supported by these results.

5.6.7 Intracortical facilitation.

Intracortical facilitation was expressed at each time point as conditioned MEP amplitude (following a 12 ms interstimulus interval) relative to non-conditioned MEP amplitude at that time point. Paired t-tests showed no significant difference between the two interventions at baseline 2 ($t(9) = 1.387$, $p = .199$) for intracortical facilitation. Mean intracortical facilitation at baseline 2 was 1.987 ($SD = 0.879$) prior to the EMG-NMES intervention, and 1.504 (SD = 0.354) prior to the voluntary activation intervention. Example conditioned MEP traces (with a 12 ms interstimulus interval) from one participant before and after the EMG-NMES intervention are presented in Figure 5.7 below.

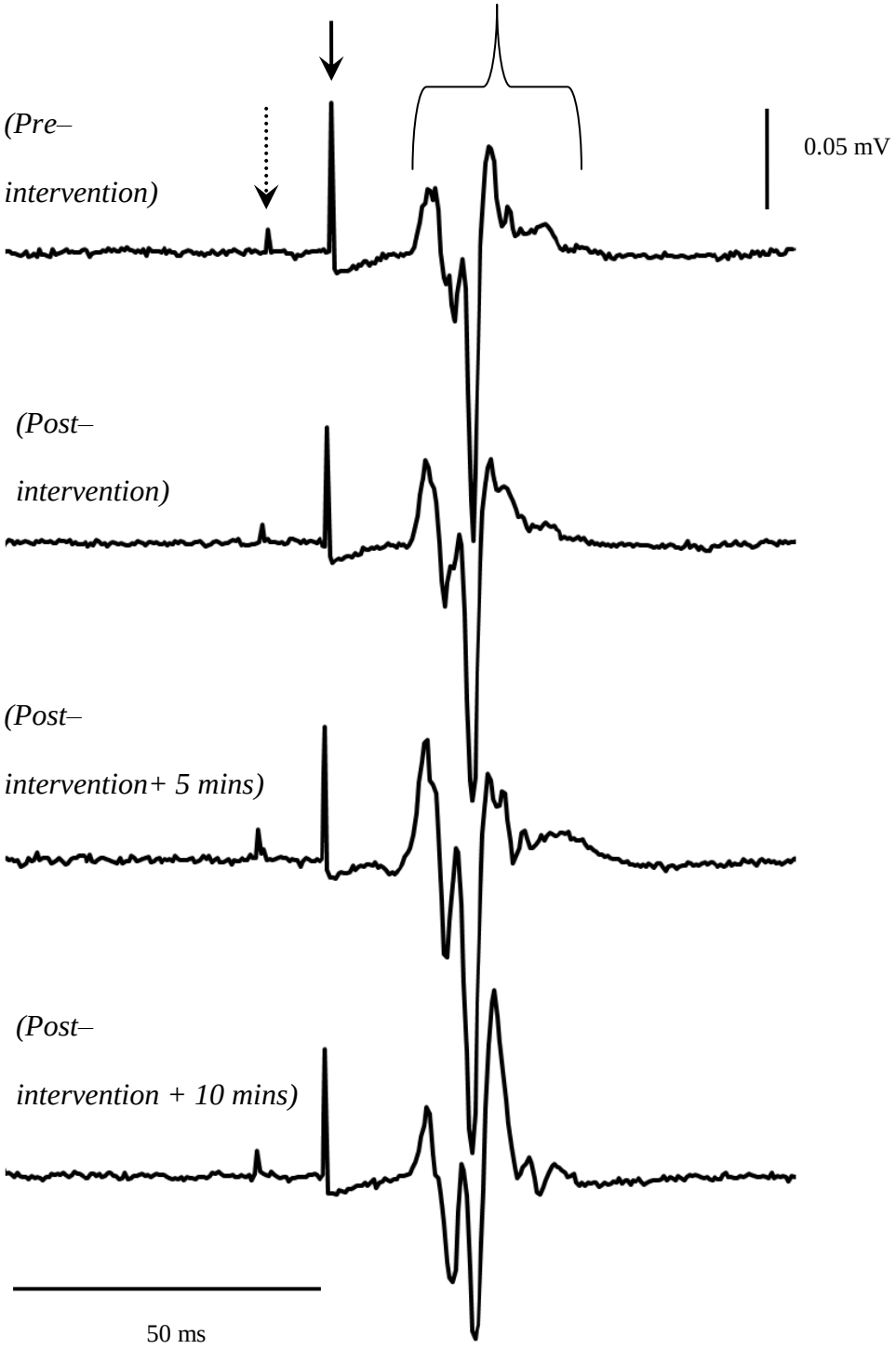


Figure 5.7. Example conditioned MEP traces (12 ms interstimulus interval) over time from one participant.

Note: This figure shows ICF by conditioned MEP amplitude over time for one participant (P3), before and after the EMG-NMES intervention. The broken arrow indicates the conditioning stimulus (80% resting threshold) for FDS 12.5 ms prior to the test stimulus (130% resting threshold). The solid arrow indicates the stimulus artefact. The bracket indicates the MEP. Traces are an average of eight responses.

Group Comparisons

Mauchly's test indicated that sphericity could be assumed for the main effect of time ($\chi^2(5) = 8.228$, $p = .148$), accordingly no correction to degrees of freedom was required. However the assumption of sphericity was violated for the interaction effect of intervention x time ($\chi^2(5) = 12.784$, $p = .027$) and degrees of freedom were therefore corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.551$ for the interaction effect of intervention x time).

There was no significant main effect of intervention ($F(1, 8) = 1.003$, $p = .346$), or time ($F(3,24) = 0.372$, $p = .774$), or interaction effect of intervention x time ($F(1.653, 13.220) = 0.632$, $p = .518$). These results are depicted graphically in Figure 5.8.

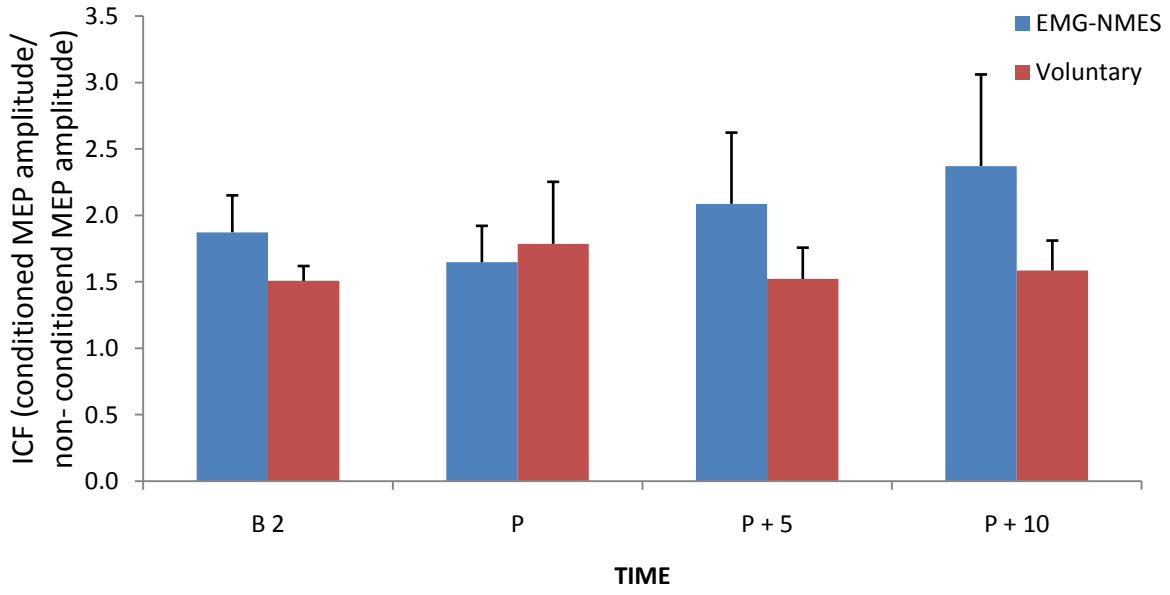


Figure 5.8. Group results for intracortical facilitation over time.

Note: Error bars show standard error of the mean. EMG-NMES = electromyography triggered neuromuscular electrical stimulation intervention, Voluntary = voluntary activation intervention, B 2 = baseline 2, P = post-intervention, P + 5 = post-intervention + 5 minutes, P + 10 = post-intervention + 10 minutes. MEP amplitude for baseline 2 and each subsequent time point was normalised to baseline 1.

Neither EMG-NMES nor voluntary activation resulted in an immediate increase in intracortical facilitation following the intervention. The hypotheses that EMG-NMES would have an enhanced effect on cortical excitability as shown by intracortical facilitation and that this effect would be greater than that resulting from the voluntary activation protocol, are not supported by these results.

5.6.8 MEP latency.

MEP latency was defined as the first point following the stimulus artefact that the EMG signal exceeded the background RMS by 3 standard deviations.

Prior to non-conditioned MEP

Paired t-tests showed no significant difference in MEP latency between test stimulus and non-conditioned MEP between baseline 1 and baseline 2 for the EMG-NMES intervention ($t(9) = -0.190$, $p = .853$) or the voluntary activation intervention ($t(9) = -0.749$, $p = .473$). Baseline 2 values have therefore been used as the pre-intervention data in the analyses of MEP latency. At baseline 2 mean MEP latency prior to the EMG-NMES intervention was 19.62 ms ($SD = 1.92$ ms). Prior to the voluntary activation intervention mean MEP latency was 19.86 ms ($SD = 2.48$ ms). Mauchly's test indicated the assumption of sphericity had been violated for the main effect of time ($\chi^2(5) = 27.625$, $p \leq .001$ and interaction effect of intervention x time ($\chi^2(5) = 21.391$, $p = .001$). Degrees of freedom were therefore corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.467$ for the main effect of time, and ($\varepsilon = 0.425$ for the interaction effect of intervention x time). There was no significant main effect of intervention ($F(1,8) = 3.614$, $p = .094$), or time ($F(1.402, 11.220) = 1.888$, $p = .199$), or interaction

effect of intervention x time (F(1.274, 10.190) = 1.065, p = .346 on MEP latency during non-conditioned assessment of MEP amplitude.

Prior to conditioned MEP (2.5 ms interstimulus interval)

At baseline 2 mean MEP latency prior to the EMG-NMES intervention was 18.36 ms (SD = 1.76 ms). Prior to the voluntary activation intervention mean MEP latency was 18.85 ms (SD = 2.70 ms). Mauchly's test indicated that sphericity could be assumed for the main effect of time ($\chi^2(5) = 2.875$, p = .722) and interaction effect of intervention x time ($\chi^2(5) = 5.710$, p = .340) accordingly no correction to degrees of freedom was required. There was no significant main effect of intervention ($F(1,8)$ = 0.038, p = .851), or time ($F(3, 24) = 0.461$, p = .712), or interaction effect of intervention x time ($F(3, 24) = 0.893$, p = .459) on MEP latency during the assessment of intracortical inhibition.

Prior to conditioned MEP (12 ms interstimulus interval)

At baseline 2 mean MEP latency prior to the EMG-NMES intervention was 18.58 ms (SD = 2.21 ms). Prior to the voluntary activation intervention mean MEP latency was 18.29 ms (SD = 1.27 ms). Mauchly's test indicated that sphericity could be assumed for the main effect of time ($\chi^2(5) = 8.740$, p = .123) and interaction effect of intervention x time ($\chi^2(5) = 6.534$, p = .262) accordingly no correction to degrees of freedom was required. There was no significant main effect of intervention ($F(1,8)$ = 0.128, p = .729), or time ($F(3, 24) = 0.292$, p = .831), or interaction effect of intervention x time ($F(3, 24) = 0.601$, p = .621) on MEP latency during the assessment of intracortical facilitation.

5.6.9 Maximal grip force.

Grip MVC was assessed in the more affected hand pre- and post-intervention. There was a significant main effect of time showing that grip MVC reduced at post-intervention (*M* = 47.9, *SD* = 12.8*)* compared to pre-intervention (*M* = 52.3, *SD* = 13.2), (*F*(1, 8) = 9.197, *p* = .16), Figure 5.9 presents this result graphically. There was no significant main effect of intervention (*F*(1, 8) = 0.20, *p* = .891), or interaction effect for intervention x time (*F*(1, 8) = 0.476, *p* = .510), on grip MVC following the assessment of cortical excitability.

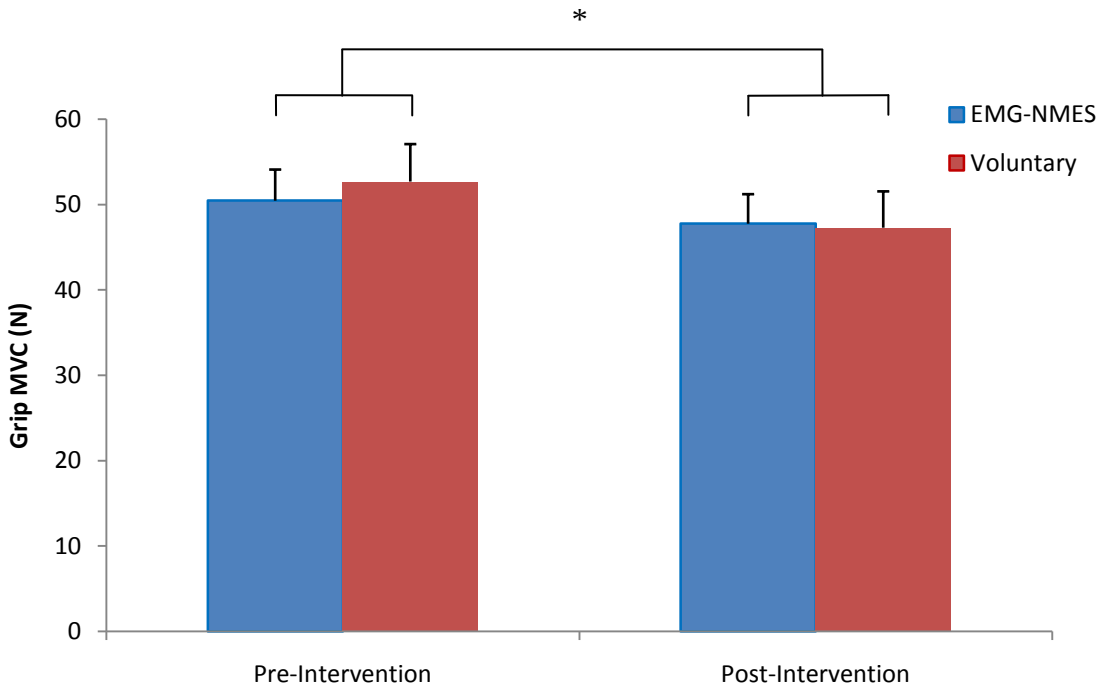


Figure 5.9. Main effect of time on mean grip MVC before and after the assessment of cortical excitability.

Note: Error bars indicate standard error of the mean, grip MVC = grip maximum voluntary contraction, EMG-NMES = electromyography triggered neuromuscular electrical stimulation intervention, Voluntary = voluntary activation intervention, N = newtons.
** $p \leq .05$*

5.7 Measures of Grip Control

5.7.1 Introduction.

Grip control was measured by calculating the root mean square error (RMSE) between the force trace and target trace. The stability of RMSE was assessed over the first eight repetitions for each task. Group comparisons were calculated comparing the best performance (lowest RMSE) pre- and post-intervention.

5.7.2 Sine wave tracking task.

Practice stability

Figure 5.10 shows the RMSE during the three practice and five pre-intervention trials of the sine wave tracking task. There was an increase in RMSE at practice 3 in consequence of one participant increasing tracking error from 1.13 N in practice 2, to 6.95 N at practice 3.

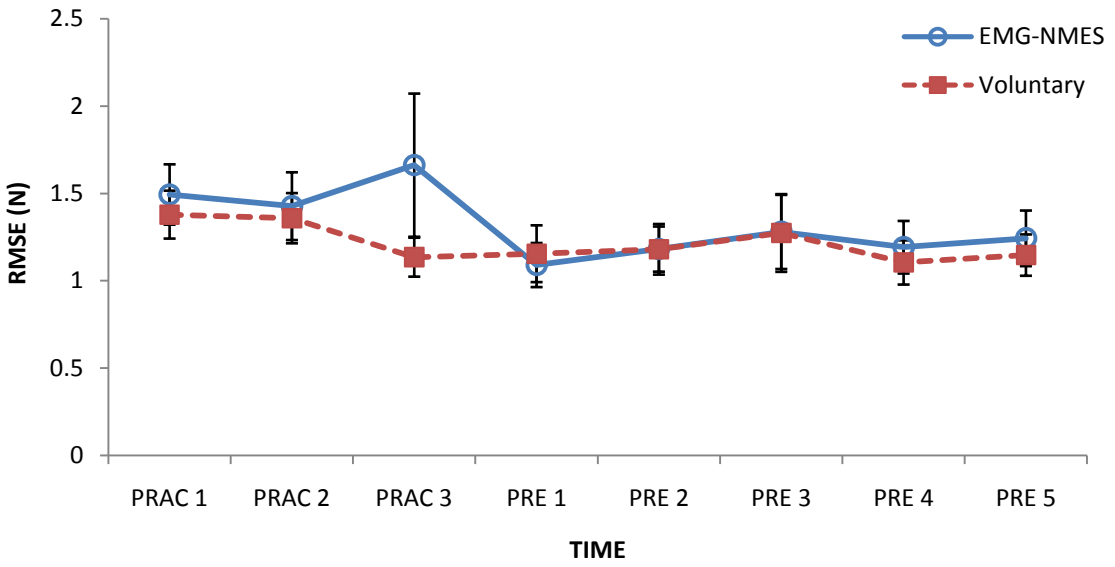


Figure 5.10. Mean sine wave root mean square error during practice and pre-intervention trials.

Note: Error bars show standard error of the mean. The blue circle data points and solid line represent the electromyography triggered neuromuscular electrical stimulation intervention; the red square data points and dashed line represent the voluntary activation intervention. Prac = practice, Pre = pre-intervention, N = newtons.

The presence of a change in RMSE over time was determined using a two-way repeated measures ANOVA. Mauchly's test indicated the assumption of sphericity was violated for the main effect of time ($\chi^2(27) = 86.004$, $p \leq .001$) and for the interaction effect of intervention x time ($\chi^2(27) = 63.015$, $p \leq .001$). Degrees of freedom were therefore corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.309$ for the main effect of time, $\varepsilon = 0.382$ for the interaction effect of intervention x time). There was no significant main effect of intervention ($F(1, 14) = 0.529$, $p = .479$), or time ($F(2.162, 30.274) = 1.660$, $p = .206$), or interaction effect of intervention x time ($F(2.674, 37.435) = 0.819$, $p = .479$) on sine wave RMSE over the eight pre-intervention trials. The ANOVA and graphed results show mean performance on the

sine tracking task was stable prior to the intervention in both the EMG-NMES and voluntary activation intervention sessions. Best performance of the five pre-intervention trials was therefore used as the measure of pre-intervention RMSE.

Group comparisons

Mean best performance for the sine wave tracking task was 0.90 N (*SD* = 0.32 N) before and 0.94 N (*SD* = 0.43 N) after EMG-NMES training. Mean best performance was 0.94 N (*SD* = 0.44 N) before and 0.92 N (*SD* = 0.61 N) after voluntary activation training. There was no significant main effect of intervention ($F(1, 14) = 0.006$, $p = .942$), or time ($F(1,14) = 0.002$, $p = .967$), or interaction effect of intervention x time ($F(1,14) = 0.357$, $p = .56$) on best performance during the sine wave tracking task. Accordingly the hypotheses that both EMG-NMES and voluntary activation during a force tracking intervention would result in improved grip performance, and that EMG-NMES would result in greater improvement in grip control, were not supported by the results for the sine wave tracking task. Figure 5.11 shows the RMSE over time for the two interventions.

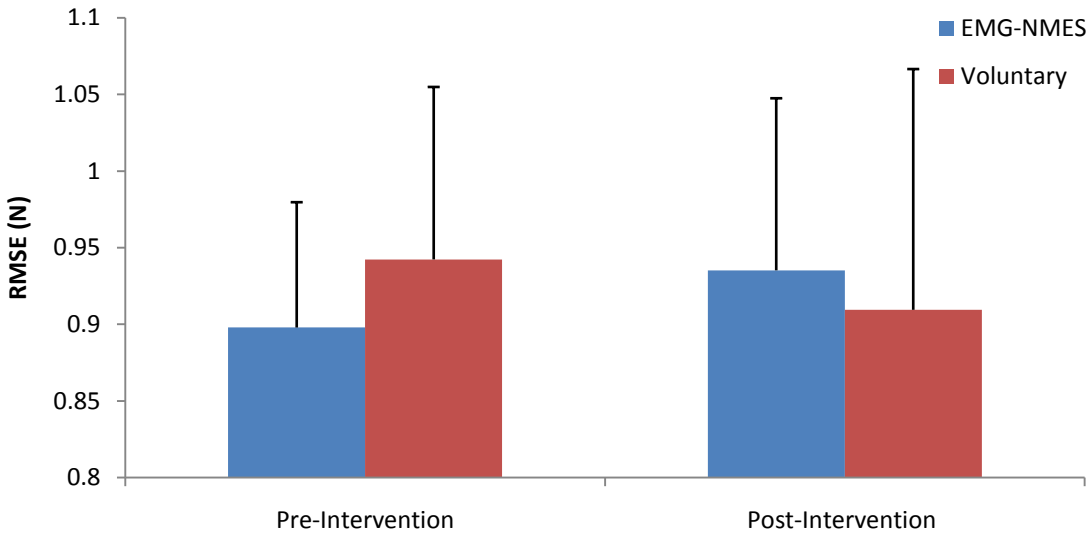


Figure 5.11. Sine wave root mean square error over time.

Note: Error bars indicate standard error of the mean, RMSE = root mean square error, EMG-NMES = electromyography triggered neuromuscular electrical stimulation intervention, Voluntary = voluntary activation intervention, N = newtons.

5.7.3 Ramp tracking task: ramp up.

Practice stability

Figure 5.12 shows the RMSE during the three practice and five pre-intervention trials of the ramp up component of the ramp tracking task. Mean performance was stable following the practice trials. The increase in RMSE during the third pre-intervention trial is the result of increased tracking error by one participant.

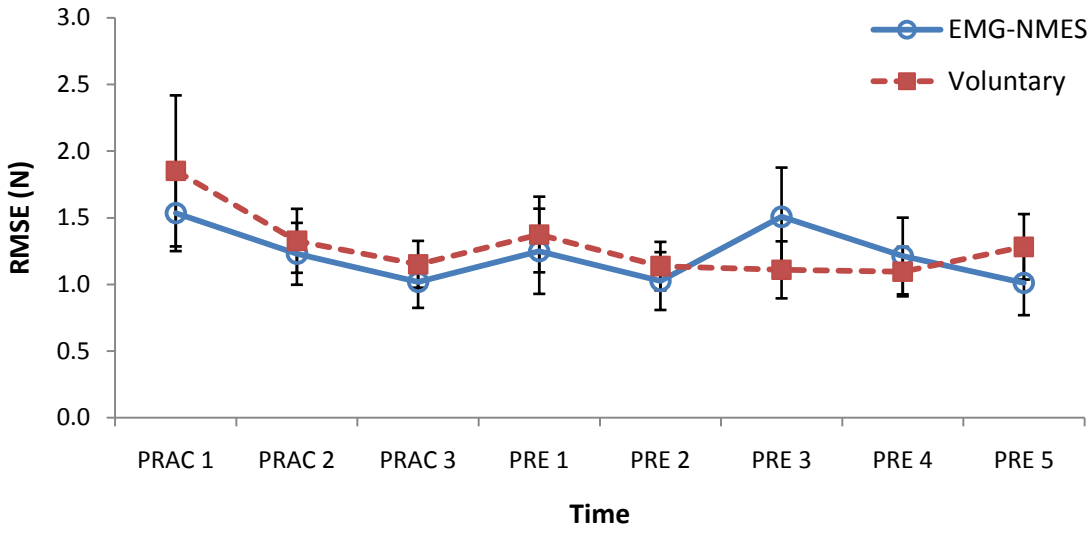


Figure 5.12. Mean ramp up root mean square error during practice and pre-intervention trials.

Note: Error bars show standard error of the mean. The blue circle data points and solid line represent the electromyography triggered neuromuscular electrical stimulation intervention; the red square data points and dashed line represent the voluntary activation intervention. Prac = practice, Pre = pre-intervention, N = newtons.

The presence of a change in RMSE over time was determined using a two-way repeated measures ANOVA. Mauchly's test indicated the assumption of sphericity was violated for the main effect of time ($\chi^2(27) = 70.942$, $p \leq .001$) and for the interaction effect of intervention x time ($\chi^2(27) = 71.202$, $p \leq .001$). Degrees of freedom were therefore corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.324$ for the main effect of time, $\varepsilon = 0.337$ for the interaction effect of intervention x time). There was no significant main effect of intervention ($F(1, 14) = 0.314$, $p = .585$), or time ($F(2.268, 29.483) = 2.282$, $p = .114$), or interaction effect of intervention x time ($F(2.359, 30.664) = 0.298$, $p = .779$) on ramp up RMSE over the eight pre-intervention trials. The ANOVA and graphed results show mean performance on the ramp up component of the ramp tracking task stabilised prior to the intervention in both the

EMG-NMES and voluntary activation intervention sessions. Best performance of the five pre-intervention trials was therefore used as the measure of pre-intervention RMSE.

Group comparisons

Mean best performance for the ramp up component of the ramp tracking task was 0 .72 N (*SD* = 0.80 N) before and 0.69 N (*SD* = 0.53 N) after EMG-NMES training. Mean best performance was 0.75 N (*SD* = 0.54 N) before and 0.66 N (*SD* = 0.43 N) after the voluntary activation training. There was no significant main effect of intervention ($F(1, 14) = < 0.000$, $p = .988$), or time ($F(1,14) = 2.112$, $p = .168$), or interaction effect of intervention x time ($F(1,14) = 0.129$, $p = .725$) on best performance of the ramp up component of the ramp tracking task. Accordingly the hypothesis that EMG-NMES and voluntary activation would improve grip control on this component of the ramp tracking task was not supported by these results.

Figure 5.13 shows RMSE over time for the two interventions.

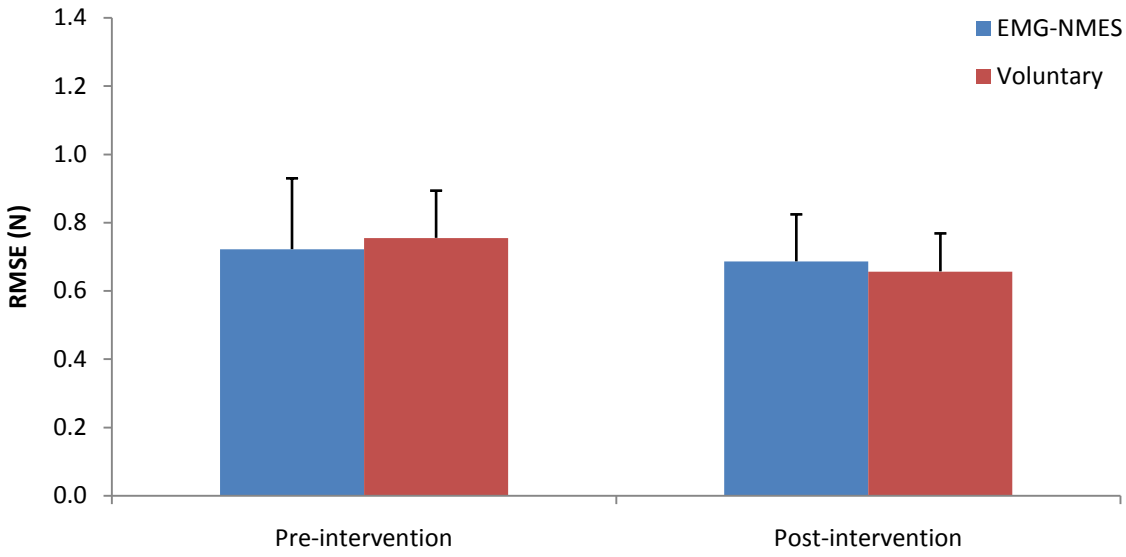


Figure 5.13. Ramp up root mean square error over time.

Note: Error bars indicated standard error of the mean, RMSE = root mean square error, EMG-NMES = electromyography triggered neuromuscular electrical stimulation intervention, Voluntary = voluntary activation intervention, N = newtons.

5.7.4 Ramp tracking task: ramp hold.

Practice stability

Figure 5.14 shows the RMSE during the three practice and five pre-intervention trials of the ramp hold component of the ramp tracking task.

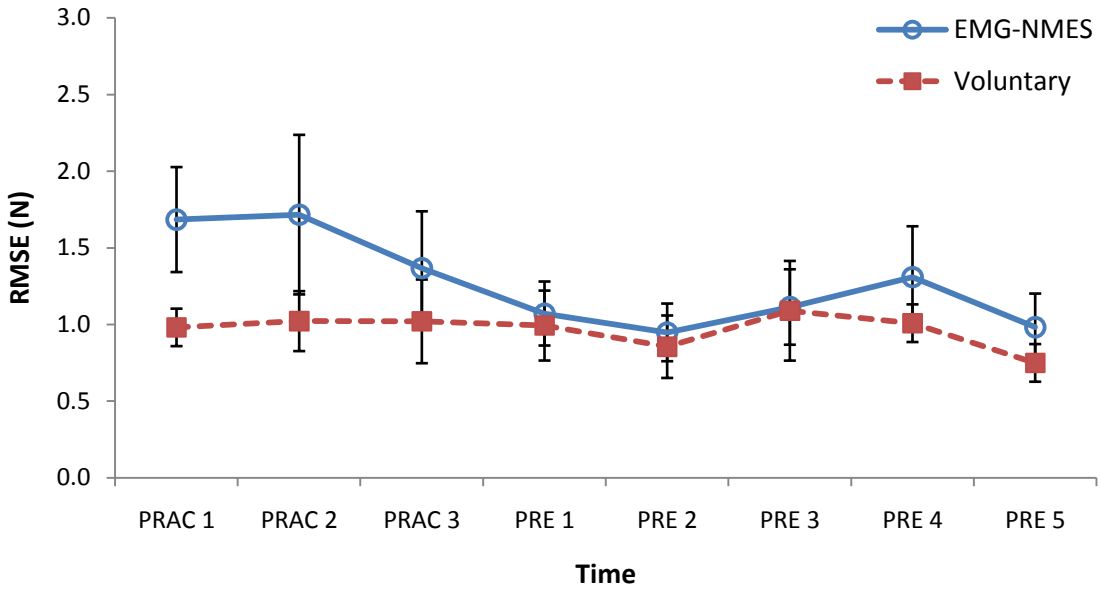


Figure 5.14. Mean ramp hold root mean square error during practice and pre-intervention trials.

Note: Error bars show standard error of the mean. The blue circle data points and solid line represent the electromyography triggered neuromuscular electrical stimulation intervention; the red square data points and dashed line represent the voluntary activation intervention. Prac = practice, Pre = pre-intervention, N = newtons.

The presence of a change in RMSE over time was determined using a two-way repeated measures ANOVA. Mauchly's test indicated the assumption of sphericity was violated for the main effect of time ($\chi^2(27) = 74.596$, $p \leq .001$) and for the interaction effect of intervention x time ($\chi^2(27) = 96.748$, $p \leq .001$). Degrees of freedom were therefore corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.333$ for the main effect of time, $\varepsilon = 0.406$ for the interaction effect of intervention x time). There was no significant main effect of intervention ($F(1, 14) = 2.013$, $p = .178$), or time ($F(2.333, 32.662) = 2.075$, $p = .135$), or interaction effect of intervention x time ($F(2.841, 39.771) = 0.957$, $p = .419$) on ramp hold RMSE over the eight pre-intervention trials. The ANOVA and graphed results show mean performance on the

ramp hold component of the ramp tracking task stabilised prior to the intervention in both the EMG-NMES and voluntary activation intervention sessions. Best performance of the five pre-intervention trials was therefore used as the measure of pre-intervention RMSE.

Group comparisons

Mean best performance for the ramp hold component of the ramp tracking task was 0.72 N (*SD* = 0.56 N) before and 0.54 N (*SD* = 0.43 N) after EMG-NMES training. Mean best performance was 0.52 N (*SD* = 0.35 N) before and 0.46 N (*SD* = 0.24 N) after the voluntary activation training. There was a significant main effect of time on best performance of the ramp hold component of the ramp tracking task ($F(1, 14) = 4.701$, $p = .048$), indicating that, across both interventions, post-intervention RMSE ($M = 0.498$, $SD = 0.347$) was lower than pre-intervention RMSE ($M = 0.617$, $SD = 0.085$); Figure 5.15 shows this reduction in error over time. There was no significant main effect of intervention ($F(1, 14) = 3.275$, $p = .092$), or interaction effect of intervention x time ($F(1,14) = 1.073$, $p = .318$), on best performance of the ramp hold component of the ramp tracking task.

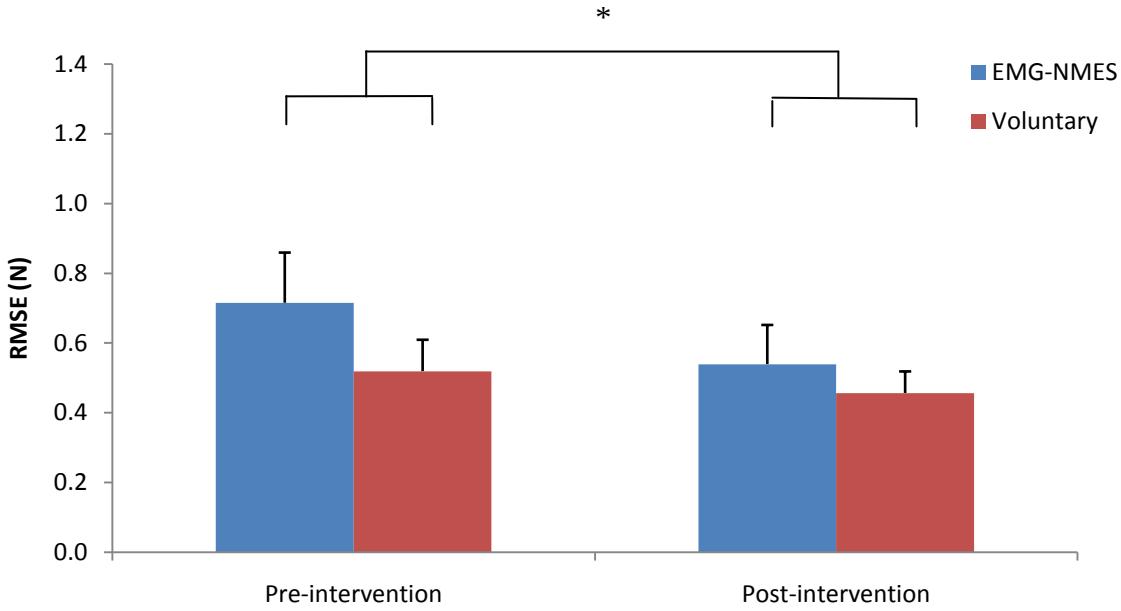


Figure 5.15. Ramp hold root mean square error over time.

Note: Errors bars indicate the standard error of the mean, RMSE = root mean square error, EMG-NMES = electromyography triggered neuromuscular electrical stimulation intervention, Voluntary = voluntary activation intervention, N = newtons.
** = $p \leq .05$*

Correlation analysis was used to identify if there was an association between participants' dexterity at baseline as measured by the Box and Block Test, and reduction in RMSE post-intervention. There was no significant correlation between Box and Block Test score for the more affected hand and increase in force tracking accuracy during the ramp hold component of the ramp tracking task after the EMG-NMES (r = -0.42, p = .263) or voluntary activation (r = -0.08, p = .841) intervention.

The hypothesis that both groups would improve in grip control on this aspect of the ramp task was supported by this result. However, the further hypothesis that EMG-NMES would improve grip control to a greater extent than the voluntary activation intervention was not supported by this result.

5.7.5 Ramp tracking task: ramp down

Practice stability

Figure 5.16 shows the RMSE during the three practice and five pre-intervention trials of the ramp down component of the ramp tracking task. RMSE was stable for this aspect of the ramp tracking task prior to each intervention.

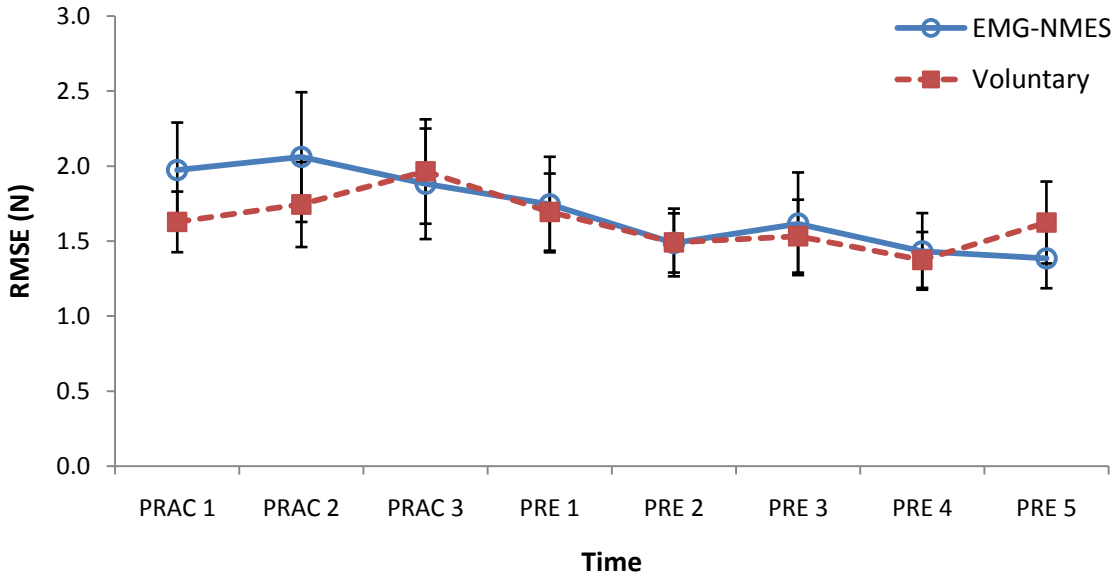


Figure 5.16. Mean ramp down root mean square error during practice and pre-intervention trials.

Note: Error bars show standard error of the mean. The blue circle data points and solid line represent the electromyography triggered neuromuscular electrical stimulation intervention; the red square data points and dashed line represent the voluntary activation intervention. Prac = practice, Pre = pre-intervention, N = newtons.

The presence of a change in RMSE over time was determined using a two-way repeated measures ANOVA. Mauchly's test indicated the assumption of sphericity was violated for the main effect of time ($\chi^2(27) = 49.899$, $p = .007$) and for the interaction effect of intervention x time ($\chi^2(27) = 49.517$, $p = .007$). Degrees of freedom were therefore corrected using Greenhouse-Geisser estimates of sphericity ($\varepsilon = 0.555$ for the

main effect of time, $\varepsilon = 0.631$ for the interaction effect of intervention x time). There were no significant main effects of intervention ($F(1, 14) = 0.61$, $p = .807$), or time ($F(3.884, 54.381) = 2.338$, $p = .068$), or interaction effects of intervention x time ($F(4.415, 61.812) = 0.634$, $p = .656$) on ramp down RMSE over the eight pre-intervention trials. The ANOVA and graphed results show mean performance on the ramp down component of the ramp tracking task stabilised prior to the intervention in both the EMG-NMES and voluntary activation intervention sessions. Best performance of the five pre-intervention trials was therefore used as the measure of pre-intervention RMSE.

Group comparisons

Mean best performance for the ramp down component of the ramp tracking task was 1.04 N (*SD* = 0.65 N) before and 0.88 N (*SD* = 0.31 N) after EMG-NMES training. Mean best performance was 1.1 N (*SD* = 0.66 N) before and 0.96 (*SD* = 0.38 N) after the voluntary activation training. There was no significant main effect of intervention ($F(1, 14) = 0.442$, $p = .517$), or time ($F(1,14) = 2.367$, $p = .146$), or interaction effect of intervention x time ($F(1,14) = 0.006$, $p = .938$) on best performance of the ramp down component of the ramp tracking task. Figure 5.17 shows RMSE over time for the two interventions.

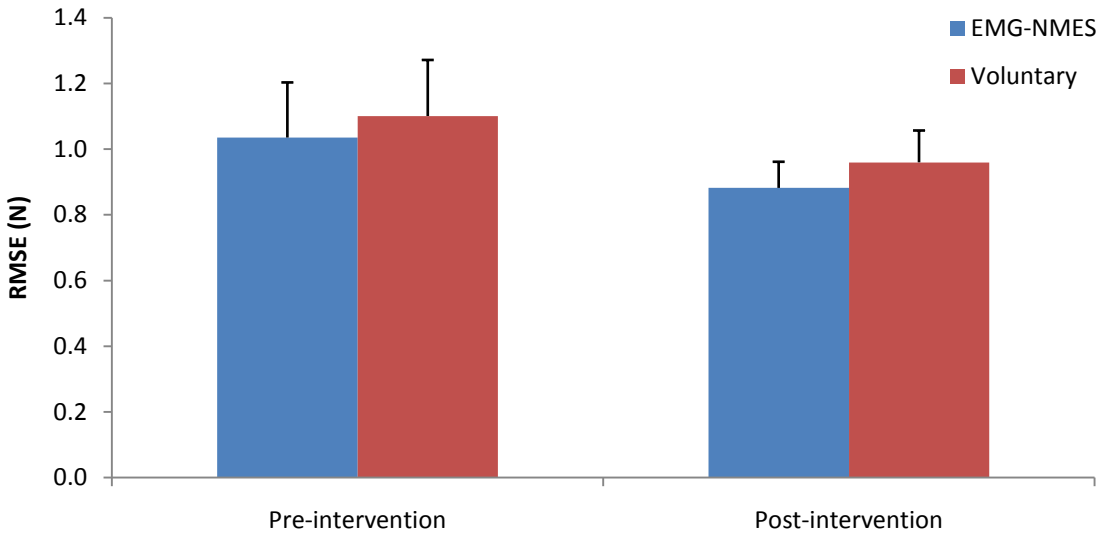


Figure 5.17. Ramp down root mean square error over time.

Note: Errors bars indicate the standard error of the mean, RMSE = root mean square error, EMG-NMES = electromyography triggered neuromuscular electrical stimulation intervention, Voluntary = voluntary activation intervention, N = newtons.

As with the sine wave and ramp up tasks, the hypothesis that both interventions would have a beneficial effect on reducing error during the tracking task was not supported by these results.

5.7.6 Maximal grip force.

Grip MVC was assessed in the more affected hand pre- and post-intervention. There was a significant main effect of time showing that grip MVC significantly reduced at post-intervention (M = 39.2, SD = 14*)* compared to pre-intervention (M = 43, SD = 14.2), ($F(1, 14) = 9.026$, $p = .009$), Figure 5.18 shows this graphically. There was no significant main effect of intervention ($F(1, 14) = 0.705$, $p = .415$), or interaction effect for intervention x time ($F(1, 14) = 0.001$, $p = .977$), on grip MVC following the assessment of grip control.

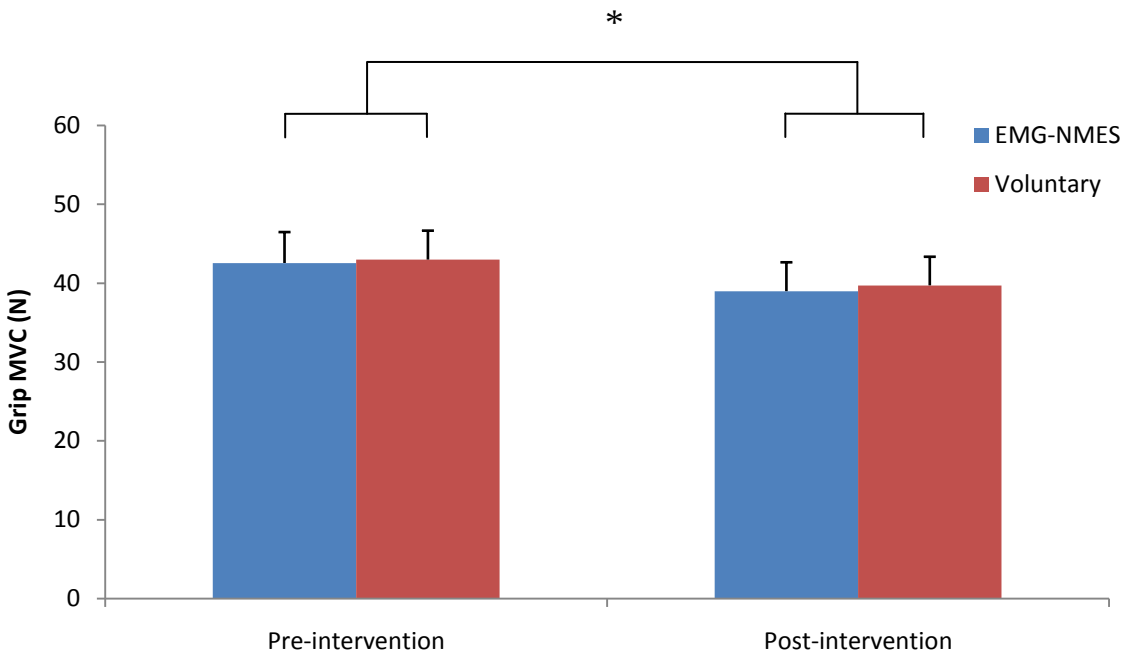


Figure 5.18. Main effect of time on mean grip MVC before and after assessment of force tracking ability.

Note: Error bars indicate standard error of the mean, grip MVC = grip maximum voluntary contraction, EMG-NMES = electromyography triggered neuromuscular electrical stimulation intervention, Voluntary = voluntary activation intervention, N = newtons.
** $p \leq .05$*

5.8 Summary of results

Background level of EMG activity was increased prior to assessment of intracortical inhibition in the EMG-NMES group, but not in the voluntary activation group. There were no significant differences in background RMS for either intervention prior to assessment of non-conditioned MEP or intracortical facilitation. The results from the measures of cortical excitability and grip control do not support the study hypotheses. No significant effects over time were found with respect to cortical excitability as measured by non-conditioned MEP amplitude or intracortical facilitation. However, intracortical inhibition increased over time in the EMG-NMES group alone,

as demonstrated by reduced MEP amplitude following the conditioned stimulus at 2.5 ms interstimulus interval. Intracortical inhibition was higher at post-intervention and at 10 minutes post-intervention compared to baseline 2 values following EMG-NMES. MEP latency did not change over time or following either intervention.

All the measured components of the grip control task were stable following the practice trials in the sine tracking and all three components of the ramp tracking task. The ramp hold component of the ramp tracking task showed reduction in tracking error over time with no difference between the two interventions. There was no change in accuracy during the sine wave tracking task and ramp ascent and descent components of the ramp tracking task over time or following either intervention. After the cortical excitability and the grip control assessments grip MVC reduced significantly; with no significant difference between the EMG-NMES and voluntary activation training interventions.

6 Discussion

6.1 Introduction

The purpose of the present study was to examine the effects on cortical excitability and grip control of a short intervention that combined either EMG-NMES or voluntary muscle activation with a grip control task. The hypotheses at the outset of the study were that both EMG-NMES and the control protocol of voluntary activation unassisted by NMES will increase cortical excitability and grip control ability in people with stroke compared to baseline measures. It was further hypothesised that the EMG-NMES intervention would result in greater changes in cortical excitability and grip control ability than the voluntary activation intervention. The results do not support the hypotheses stated.

Intracortical inhibition significantly increased following the EMG-NMES intervention. This change was in the opposite direction to that expected under the study hypotheses. The increase in intracortical inhibition was despite a slight increase in background RMS prior to the conditioned stimulus in the EMG-NMES group alone. The change in intracortical inhibition did not correspond to any change in non-conditioned MEP amplitude.

Both interventions resulted in a significant reduction in error in the force tracking task at post-intervention, but in one component of the task, during the ramp hold phase, only. There were no significant changes in error during the sine wave task or during the ramp up or ramp down components of the ramp task, and no significant difference in effect of either intervention on any of the force tracking tasks. Following

both interventions there was a significant reduction in grip strength, with no significant difference between the two interventions.

In this chapter, the results of this study with respect to cortical excitability and grip control are discussed and compared in turn with those reported in previous related studies. As sample characteristics and methods may have influenced the study findings, these factors will be discussed in relation to the results; possible explanations as to the key findings are drawn from current literature regarding neuroplasticity in chronic stroke populations. Limitations in the methods of the current study and areas for future research will be identified in the course of this discussion.

6.2 Cortical excitability

Contrary to the study hypotheses, a short intervention of EMG-NMES or voluntary activation of the target muscles did not result in any increase in cortical excitability as measured by increased MEP amplitude or intracortical facilitation, reduced intracortical inhibition, or reduced MEP latency. The primary conclusion from the results of this study is that EMG-NMES did not increase cortical excitability in the target muscle. The results of the current study concur with the results of other studies that have observed no increases in cortical excitability in populations of participants with stroke following 30 minute (Lewis & Byblow, 2004a), or longer duration (McDonnell et al., 2007; Sawaki et al., 2006; Turton & Butler, 2004) interventions. Increases in cortical excitability have, however, been observed following peripheral nerve stimulation in conjunction with motor training in people with chronic stroke (Celnik, Hummel, Harris-Love, Wolk, & Cohen, 2007).

In addition to the lack of increase in cortical excitability found in the current study, intracortical inhibition increased following the EMG-NMES intervention alone. That intracortical inhibition increased is a finding in the opposite direction to that postulated by the study hypotheses. The increase in intracortical inhibition occurred immediately post-intervention, and at ten minutes post-intervention. Increased intracortical inhibition has been observed previously in chronic stroke patients post-intervention (Hamzei et al., 2006). The increase in intracortical inhibition in the current study occurred despite higher background EMG preceding the assessment of intracortical inhibition prior to the EMG-NMES intervention alone. Intracortical inhibition would be expected to reduce in the lesioned hemisphere with higher background muscle activity of the contralesional hand (Ashby, Reynolds, Wennberg, Lozano, & Rothwell, 1999; Reynolds & Ashby, 1999; Ridding et al., 1995). The increase in intracortical inhibition occurred without any contemporaneous change in non-conditioned MEP amplitude following the EMG-NMES intervention. This is not a novel finding as significant changes in intracortical inhibition have been previously observed without significant changes in non-conditioned MEP amplitude (Celnik et al., 2007; Hamzei et al., 2006). Possible explanations for the increase in intracortical inhibition found in the current study will be discussed in further detail below.

6.2.1 Sample characteristics and cortical excitability.

Sample characteristics may be a contributing factor to why no increase in cortical excitability was found following the interventions in the current study. As MEP amplitude reduces significantly with aging (Oliviero et al., 2006), the age of participants in each study may influence the results found. The participants in the current study were older (M = 70, SD = 9 years, range 52 – 84 years), than the participants in the study by

Celnik et al. (2007) (*M* = 55, *SD* = 14, range 35 – 73 years), and more similar in age to those in McDonnell et al. (2007). Brain activity in regions involved with hand function has been found to reduce with greater duration of time elapsed since stroke (Lindberg, Schmitz, Engardt, Forssberg, & Borg, 2007), although another study has found increased MEP amplitude in chronic compared to sub-acute stroke participants (Brouwer & Schryburt-Brown, 2006). Chronicity may therefore be a further factor that alters the extent of change in cortical excitability observed. On average, time since stroke was longer (*M* = 54, *SD* = 50 months, range 9 – 196 months) for participants in the current study, than those in the study by Celnik et al. (2007), (M = 38, SD = 19 months, range 24 – 72 months).

Lesion location can influence results of cortical excitability measures. In the study by Celnik et al. (2007), an increase in cortical excitability was observed in a population of participants with sub-cortical chronic stroke. The extent of changes in cortical excitability following rehabilitation training is dependent on the degree to which M1 is intact (Hamzei et al., 2006). In the study by Hamzei et al. (2006), six people with chronic stroke (of a similar age to those in the present study) received constraint induced therapy comprising restraint of the less affected hand in conjunction with intensive daily motor task training. In order to participate in constraint induced therapy, all participants had some intact hand and finger movement. While all participants significantly improved in motor function as measured by the Wolf Motor Function Test, two distinct patterns of post-intervention response were observed cortically. In three participants, activation in the ipsilesional sensorimotor cortex significantly reduced, in conjunction with a significant decrease in intracortical inhibition in the lesioned cortex. In the remaining three participants, the opposite

response occurred post-intervention; the peaks and extent of activity in the ipsilesional sensorimotor cortex increased significantly, and intracortical inhibition in the lesioned M1 also significantly increased. The authors identified that the latter group of participants had a greater degree of involvement of the M1 hand knob and/or interruption of the outgoing fibres from the hand knob due to lesions of M1 or the internal capsule.

The location of the lesion may also have different effects on cortico-motor excitability and intracortical inhibition and facilitation (Renner, Schubert, & Hummelsheim, 2007). In the study by Renner et al. (2007), 5 minutes of active wrist and finger movement resulted in no changes in non-conditioned MEP amplitude or intracortical inhibition in participants with cortical lesions; intracortical facilitation significantly increased in the participants with sub-cortical lesions alone. While generalising results from these two small non-randomised controlled trials should be approached with caution, the results in the studies by Renner et al. (2007) and Hamzei et al. (2006) indicate the importance of identifying as far as practicable the extent and location of lesion following stroke to aid the interpretation of results.

Participants in the current study were selected on the basis of having a single unilateral stroke, and lesion location was not screened. Participants had to have some intact corticospinal connections in order to elicit or identify a cortical response from the target muscles. However, as information on site of lesion (other than side of resulting hemiplegia) was not collected, the extent to which lesion extent and location may have influenced the results in this group of participants is unknown. Age, chronicity and the location and the extent of participants' lesions may therefore have contributed to the

high variability of the data in the present study, and the lack of significant increase in cortical excitability found.

6.2.2 Task parameters and cortical excitability.

Repetitive movement on its own increases MEP amplitude in healthy adults (Pascual-Leone et al., 1995). Greater increases in MEP amplitude are seen in healthy adults following EMG-NMES compared to voluntary movement protocols (Barsi, Popovic, Tarkka, Sinkjær, & Grey, 2008; Taylor et al., 2008). Targeted upper limb rehabilitation following stroke has been shown, by meta-analysis, to result in increased excitation and activation of the lesioned hemisphere (Richards, Stewart, Woodbury, Senesac, & Cauraugh, 2008). Intensive (18 – 20 sessions) tracking training has resulted in increased activation of the lesioned hemisphere in participants with chronic stroke, and improvement in functional scores (Carey et al., 2002). There is accordingly sound rationale for the hypothesis that an intervention combining voluntary activation of the flexor muscles with EMG-NMES during a tracking training task would have more positive effects on cortical excitability than voluntary activation of the target muscle alone.

In the current study, a short intervention of two sets of 30 repetitions was used, resulting in approximately 12 minutes of exercise. There may be a minimum duration of stimulation required to elicit changes in cortical excitability. In healthy adults, one minute's stimulation of the median nerve has found to be insufficient to elicit changes in cortical excitability (Bonato et al., 1996). However, protocols of as little as 10 – 15 minutes of peripheral stimulation and EMG-NMES have resulted in increased cortical excitability in healthy adults (Hamdy et al., 1998; Taylor et al., 2008). An increase in

cortical excitability in the lesioned hemisphere has been observed following a single 1.5 hour session of physiotherapy in people with acute stroke (Liepert, Graef et al., 2000).

The effect of very short durations of EMG-NMES, NMES or peripheral stimulation has not been well investigated in people with chronic stroke. Studies that have shown an increase in cortical excitability in people with chronic stroke, following interventions using electrical stimulation of nerve or muscles, have involved longer duration stimulation and longer duration interventions than that employed in the current study (Celnik et al., 2007; Fritz, Chiu, Malcolm, Patterson, & Light, 2005). Two hours of peripheral nerve stimulation of the hand prior to an hour of motor training (repetitions of the Jebsen Taylor Hand Function Test) immediately reduced intracortical inhibition in participants with sub-cortical chronic stroke (Celnik et al., 2007). While intracortical inhibition significantly reduced post-intervention in the peripheral stimulation group alone, intracortical facilitation significantly increased following both peripheral stimulation and sham stimulation performed in conjunction with motor training (Celnik et al., 2007). There was no significant change in non-conditioned MEP amplitude at post-intervention in either training group. This work has not been replicated in participants with cortical lesions. However, even with longer duration stimulation or intervention periods, functional improvements do not always correspond with effects on cortical excitability. Significant functional improvements in some participants, following electrical stimulation and other interventions, have occurred in the absence of observed changes cortically (Lewis & Byblow, 2004a; McDonnell et al., 2007). Conversely, increased excitability and enlargement of areas of cortical excitability may occur without being reflected in improvements in functional tests (Wittenberg et al., 2003). In a study by McDonnell et al. (2007), significant

improvements in participants' grip-lift profile were observed after nine two-hour sessions of peripheral nerve stimulation and task specific training. This occurred without any significant change in cortico-motor or intracortical excitability. As the participants in the current study were of a similar age, but more chronic than those in McDonnell et al. (2007), sample characteristics and variability within participant results may have contributed to the lack of change in cortical excitability in both studies. Alternative explanations for the lack of significant change in cortical excitability will be discussed in further detail below. The short duration of intervention therefore appears to be a potential contributing, but not sole, factor in the lack of increase in cortical excitability seen in the current study.

6.2.3 Where are changes in cortical excitability occurring?

There is good evidence that the observed diminution of MEP amplitude produced by a sub-threshold conditioning stimulus preceding a test stimulus predominately occurs due to intracortical mechanisms (Di Lazzaro et al., 1998; Kujirai et al., 1993; Nakamura et al., 1997). Contributions from sub-cortical or spinal mechanisms cannot however be ruled out (Chen, 2004). As non-conditioned MEP amplitude measures cortico-motor excitability (Barker, Jalinous, & Freeston, 1985), any changes in motoneuron excitability occurring at a sub-cortical or spinal level would have been reflected by a reduction in the non-conditioned MEP amplitude. This did not occur in the current study; intracortical inhibition alone increased following EMG-NMES.

An explanation that is more plausible, and consistent with the results found in the study by Hamzei et al. (2006), is that measuring MEP amplitude over a single site in the lesioned M1 will not address the possibility that neural changes in response to the

intervention may be happening in secondary areas or in the non-lesioned hemisphere. This would be one explanation why assessment of MEP amplitude did not identify increases in cortical excitability in the current study. The methods used here also meant that it was not possible to observe any increases in cortical excitability or activity that may have been occurring in other brain regions in conjunction with the increase in intracortical inhibition (Hamzei et al., 2006).

The extent of the excitable cortical area may be altered following a motor training intervention, rather than the excitability of the hotspot for the target muscle. Altering the methods to include TMS mapping, rather than measuring MEP amplitude at a single site, would be required to identify if this was the case in the current study. In acute stroke patients, enlargements in motor map in the lesioned hemisphere have been observed in conjunction with improved function following a single physiotherapy session, but individual responses still may be highly variable (Liepert, Graef et al., 2000). A medial shift of the cortical map may be more reliable in predicting recovery and measuring increases in cortical excitability in response to training than changes in MEP amplitude at the hotspot (Platz et al., 2005).

Changes in cortical excitability following an intervention in people with stroke may also be occurring in secondary regions of the lesioned hemisphere or in the non-lesioned hemisphere (Carey et al., 2002; Kimberley et al., 2004; Ward et al., 2007). This may occur in particular when the stroke involves more of the lesioned motor cortex (Hamzei et al., 2006). Assessing both hemispheres using TMS (Lewis & Byblow, 2004b) or combining neuroimaging techniques (Blickenstorfer et al., 2009; Hamzei et al., 2006; Kičić, Lioumis, Ilmoniemi, & Nikulin, 2008; Rossini et al., 2007) may

therefore be required to provide a complete analysis of the cortical effects of stroke and responses during recovery and rehabilitation.

It has been observed in healthy populations that cortical excitability and area of excitability may reduce following skill consolidation (Meister et al., 2005). This is an explanation that McDonnell et al. (2007) provide for not observing changes in cortical excitability following their 18 hour intervention, and is consistent with the significant functional improvement they found in grip control. In the current study grip control was assessed in separate sessions to cortical excitability, and results for each outcome measure were highly variable; this limits the ability to identify any association between neural changes and changes in the functional measure of interest.

Changes in cortical excitability in the current study may also have been occurring with respect to muscles other than FDS. High frequency electrical stimulation has been shown to increase the excitability of the motor area representing the antagonist, non-stimulated, muscle in healthy adults and in participants with writer's cramp (Mima et al., 2004; Tinazzi et al., 2005; Tinazzi et al., 2006). High frequency, wide pulse width transcutaneous electrical nerve stimulation of the wrist flexors for 30 minutes at low intensity resulted in a significant reduction in MEP amplitude of the stimulated finger flexors, and significant increases in the MEP amplitude of finger extensor muscles (Tinazzi et al., 2005). A single, not paired-pulse, TMS protocol was used; however, as there were no significant changes observed in H-wave or maximal peripheral M-wave responses in the flexors, the authors propose a cortical effect of the stimulation was likely. These cortical inhibitory changes with respect to finger flexors, and facilitatory changes in the extensors, persisted for approximately half an hour. No impairment or functional measures were taken in the study by Tinazzi et al. (2005). One

unintended possible consequence of the EMG-NMES parameters used in the current study may be to facilitate use of the hand and finger extensor muscles where there is disruption of descending inhibition to the flexors. One participant in the current study (P2) reported greater finger extension ability following the EMG-NMES intervention. The results from this participant show that intracortical inhibition increased in FDS at post-intervention compared to baseline 2 following both EMG-NMES and voluntary activation interventions; the improvement in hand opening reported by P2 cannot from these results be attributed to EMG-NMES. These changes in intracortical inhibition did not correspond to any reduction in non-conditioned MEP amplitude in this participant. In the present study, insufficient EMG data were collected from the extensors to identify if there was any increase in cortical excitability in the motor area representing P2's extensor muscles. EMG activity was monitored to ensure that cortical excitability was assessed while FDS and the superficial finger extensor muscles were at rest. To assist this, participants' hands were positioned in their laps or supported on pillows as required to reduce the amount of EMG activity, with particular attention to FDS. A resting state in the extensor muscles was difficult to obtain contemporaneously with FDS at rest, resulting in most extensor MEP traces having to be discarded. It may be that the resting position of the hand during TMS elicited activation of the extensor muscles.

Any possible cortical excitatory effect of the EMG-NMES parameters on the extensor muscles is likely to have been attenuated by the cognitive and volitional demands of the training task in the current study (Carey et al., 2007; Kimberley et al., 2004). The current study protocol elicited activation of the finger flexors with the EMG-NMES, and the finger flexors were active during the training task. The task also

required participants' attention, distinguishing the intervention from the passive methodologies employed in Mima et al. (2004) and Tinazzi et al. (2006). The potential for EMG-NMES to have disparate effects depending on stimulation parameters does, however, highlight both the importance of providing sound rationale for parameters used, and the need to more thoroughly explore the effects cortically and functionally of these different parameters in neurological populations.

Muscle fatigue following peripheral nerve stimulation has been observed to cause MEP depression in healthy adults (Pitcher & Miles, 2002; Todd, Taylor, & Gandevia, 2003). The presence of muscle fatigue as evidenced by significantly reduced grip MVC following both the EMG-NMES and voluntary activation interventions may be one reason why there was no increase in cortical excitability seen in the current study following either intervention.

6.2.4 TMS parameters.

Intracortical inhibition is measured in relation to non-conditioned MEP amplitude, and will therefore alter with the size of the non-conditioned MEP. In some studies, this effect has been controlled for by adjusting TMS stimulator output intensity to produce a specified MEP amplitude in order to obtain a consistent level of cortical stimulation (Liepert, Dettmers, Terborg, & Weiller, 2001; Rosenkranz & Rothwell, 2006). However, changing the intensity of the test stimulus by altering TMS stimulator output intensity also influences the amount of intracortical inhibition (Garry & Thomson, 2009; Zoghi, Pearce, & Nordstrom, 2003). In the current study, test stimulus intensity was kept constant across time periods at 130% RTh, and not adjusted to maintain a constant level of cortical stimulation; this approach has also been adopted in other studies (Benwell et al., 2006; Thomson, Garry, & Summers, 2008). It has recently

been observed in healthy adults that the extent of intracortical inhibition is more likely to alter if TMS stimulator output is increased than if MEP amplitude changes (Garry & Thomson, 2009). While the effect on intracortical inhibition of maintaining a constant level of cortical stimulation, as opposed to constant stimulator output intensity, has not been tested in neurologically impaired populations, the study by Garry et al. (2009) suggests that the approach taken in the current study is less likely to influence intracortical inhibition than if the alternative method was used. From the results it appears that the choice of TMS methods was appropriate in the current study as MEP amplitude remained constant over time. Monitoring recruitment curves at a range of test and conditioning stimulus intensities would be one means of reducing any confounding influence on intracortical inhibition of the choice of keeping either stimulus intensity or level of cortical stimulation constant (Bütefisch et al., 2003; Lotze, Braun, Birbaumer, Anders, & Cohen, 2003; Reis et al., 2008; Rothwell, Day, Thompson, & Kujirai, 2009). As recruitment curve and mapping procedures take longer to implement, using these methods may have missed the immediate post-intervention changes sought to be captured in the current pilot study using single and paired-pulse TMS. These alternative methods of measuring cortical excitability using TMS would however be appropriate in future studies when examining longer duration interventions and effects.

Background EMG was monitored to ensure that any changes in MEP amplitude could be attributed to changes in cortico-motor excitability and not influenced by the amount of activity in the muscle (Fisher, Nakamura, Bestmann, Rothwell, & Bostock, 2002; Ridding et al., 1995; Roshan, Paradiso, & Chen, 2003). Background EMG was quiet in all time periods except prior to the assessment of intracortical inhibition in the EMG-NMES group alone. In the absence of any change in conditions or instructions

prior to the conditioned stimulus being applied, and given the randomised nature of stimulus delivery, the change in background RMS is likely to be either an error in discarding MEP traces, or a consequence of the high degree of variability in cortical excitability in the study participants. Any error in choice of MEPs to discard would be reduced by setting *a priori* a fixed level of background muscle activation for all participants as a threshold for discarding MEP traces (Stinear, Barber, Coxon, Fleming, & Byblow, 2008), rather than via visual inspection of MEP traces on a participant-by-participant basis as was done in the current study. As MEPs are more variable in the relaxed state, incorporating a low level muscle contraction may have reduced the degree of variability seen in background RMS and cortical excitability (Kiers, Cros, Chiappa, & Fang, 1993). Adjusting the level of voluntary activation may however mask any changes in cortical excitability evoked by the intervention (Fisher et al., 2002; Ridding et al., 1995; Roshan et al., 2003).

6.2.5 Cortical excitability summary.

There was no increase in cortical excitability following EMG-NMES or voluntary activation interventions in the current study. Training duration, lesion location and the possibility that changes in excitation were occurring at cortical sites distant from the hotspot are likely contributors to the lack of increase in excitability seen following the interventions. With large variability in measures of cortical excitability in this population, and inherent in the assessment of cortical excitability following stroke, it is also possible the present study was insufficiently powered to identify anything other than very large changes in these measures. The results from the current study and from the studies by McDonnell et al. (2007), Hamzei et. al. (2006) and Renner et al. (2007), suggest that more comprehensive measurement techniques may contribute greater

information regarding the effects of interventions on cortical excitability following stroke. This is particularly the case when M1 is significantly involved or, as in the current study, the extent and location of the lesion is unknown. In order to identify immediate and prolonged effects of EMG-NMES training both cortically and functionally, the methods used in the current study would need to be altered. Including a post-intervention functional outcome measure contemporaneous with monitoring changes in cortical excitability in both hemispheres during and after training would better capture any immediate effects that may be occurring cortically and functionally due to skill acquisition, and subsequently due to skill consolidation.

6.3 Grip control

After a very brief intervention, participants with chronic stroke improved their ability to keep grip forces stable. This was indicated by a 25% reduction in RMSE, on average, measured during the ramp hold component of the ramp tracking task. In the present study, the training task required participants to increase grip to 8.5 N and hold grip steady at this level for 6 seconds before resting. The improvement in grip control in the current study occurred in the ramp hold aspect of the test task alone; one reason for this may be that this aspect of the test tasks most closely resembled the training. There were no significant changes in any other aspect of the tracking tasks, or any significant difference between the EMG-NMES and voluntary activation interventions. Repetition of the force tracking training task appeared sufficient alone to elicit this improvement. The hypothesis that EMG-NMES would result in greater improvements in grip control is therefore not supported by the results.

EMG-NMES of the wrist extensors compared to passive NMES in participants with chronic stroke resulted in no significant functional improvements after 6 weeks (de Kroon & Ijzerman, 2008). This result highlights that it is likely, if the objective of the intervention is to improve function, that combining EMG-NMES with functional training is required (Kimberley et al., 2004). The rationale for using EMG-NMES in conjunction with grip control training in the current study was to enhance motor learning by increasing afferent input in conjunction with facilitating motor output (Rushton, 2003). Accordingly, participants' training involved EMG-NMES or voluntary activation of the finger flexor muscles during a simple and short duration multi-digit tracking training task. In other studies, participants with chronic stroke have been able to improve in tracking ability following repetition of tracking tasks, albeit for longer training periods than in the current study, by what appear to be larger margins; and transfer the improved tracking ability achieved following training to dissimilar force tracking tasks (Kriz et al., 1995; Kurillo, Gregoric et al., 2005; Kurillo et al., 2004). Participants in the current study were unable to transfer training ability, as shown by the lack of improvement in the randomly generated sine wave task either between interventions or over time. This may be due to sample characteristics and/or greater variability in tracking performance in the current participants compared to previous studies; duration of training and task parameters may also have influenced the results.

6.3.1 Sample characteristics and grip control.

Comparing the participants in this study with those in other studies that have looked at interventions to improve grip control following stroke (Alberts et al., 2004; Aruin, 2005; Dafotakis et al., 2008; Frick & Alberts, 2006b; Kriz et al., 1995; Kurillo, Gregoric et al., 2005; Kurillo et al., 2004; McDonnell et al., 2007; Rosenstein et al.,

2008), the participants in the current study were older than all but those in one study. In McDonnell et al. (2007), participants in the peripheral stimulation group had a similar mean age (M = 71, SD = 11 years) and a wider range of ages (57 – 94 years) to those in the present study (M = 70, SD = 9 years, range 52 – 84 years). Improved grip control observed in studies other than that of McDonnell et al. (2007), may not have been duplicated in the current study in part due to the confounding factor of pre-existing age-related decrements in grip control likely to be present in the older population assessed (Ranganathan et al., 2001).

Time elapsed since stroke was longer for participants in the current study than in previous force tracking studies, and other studies that have assessed the effect of interventions on grip control in participants with chronic stroke (Alberts et al., 2004; Kriz et al., 1995; Kurillo, Gregoric et al., 2005; Kurillo et al., 2004; Rosenstein et al., 2008). Poorest performance in grip control and following tracking training has been observed previously in the oldest and most chronic participants (Kurillo, Gregoric et al., 2005). The presence of a partial improvement in grip control only following the interventions in the current study may therefore have been influenced by the age and chronicity of participants.

Participants with lesions of the posterior limb of the internal capsule have been found to have particularly poor ability to form and stabilise grip, although sensation and strength may be mildly affected or close to normal (Wenzelburger et al., 2005). Lesion location may therefore have affected the results found with regard to grip control. Two participants in the current study (P10 and P13) took part in the grip control limb of the study alone as MEPs could not be elicited. This suggests stroke affected the hand area of these participants more (whether due to greater involvement of M1 or a sub-cortical

lesion preventing relay of descending messages) than the participants whose cortical excitability was able to be assessed. However some, but not all, aspects of hand function were more affected in these two participants than those who were able to take part in the TMS assessment and the group of participants as a whole. Both participants 10 and 13 had very weak grip strength in the affected hand; 16 and 26 N respectively lower than the group mean grip MVC (M = 43.3, SD = 15.6). Participant 13 had the poorest dexterity in the more affected hand of all participants, with a Box and Block Test score of 6 blocks compared to the group mean of 38 (SD = 16). Participant 10's Box and Block Test score for the more affected hand at 39 blocks slightly exceeded the group mean. Box and Block Test scores in these participants did not appear to predict or preclude improvement in best performance on the force tracking tasks. For example, group mean improvement in best performance on the ramp hold task following the EMG-NMES intervention was approximately 25%. Participant 10's best performance didn't change following the EMG-NMES session compared to pre-intervention. However, Participant 13, with the lowest dexterity score of the group, reduced tracking error at post-intervention in this aspect of the ramp task by close to 75%. Participant 13 did not improve in ramp hold ability following the voluntary activation task. While these individual results suggest that force tracking training (and the EMG-NMES intervention) may have greatest benefits for grip control in participants with poorer functional dexterity, for participants overall, there was no significant correlation between Box and Block Test score and increase in force tracking accuracy during the ramp hold component of the ramp tracking task after either intervention.

Functional ability at baseline may have influenced the high variability in grip control performance and the partial improvement in tracking accuracy found in the

current study. Function in the more affected hand was impaired relative to the less affected hand as shown by significant differences in dexterity and strength. The less affected hand was also affected as shown by reduced grip MVC compared to healthy older adults of a similar age (Bohannon et al., 2006). Grip MVC in the current study ranged between 13 N and 33 N for the more affected hand. Dissimilar methods of measurement make comparison of grip MVC in the current and other studies that have assessed grip control following stroke approximate only. During a multi-digit grip task, maximal forces measured via a force transducer appear to be on average twice the grip strength recorded in the more affected hand of the current participants (Kurillo, Goljar et al., 2005b). The participants in this study therefore appear to have considerable grip weakness compared to other people with stroke when this was assessed at maximal level.

Weak grip MVC in the current study did not appear to negatively impact dexterity compared to other participants with chronic stroke. The participants in the present study had, on average, better performance on the Box and Block Test than baseline performance of participants in other studies that have used in this test in assessing the effect of electrical stimulation on hand function following stroke (Alon, Levitt, & McCarthy, 2007; Bhatt et al., 2007; Cauraugh & Kim, 2003a; Kimberley et al., 2004; Knutson, Harley, Hisel, & Chae, 2007; Shin et al., 2008). Despite better dexterity at baseline, participants in the current study did not improve in most aspects of grip control following the interventions. These results suggest a complex relationship between maximal grip strength, ability to control grip during dextrous functional tasks as required by the Box and Block Test and the isometric demands of the force tracking tasks examined here.

6.3.2 Task parameters and grip control.

While the force tracking tasks used in the current study do not exactly duplicate those used previously, participants' accuracy in the current study was lower than healthy adults during a sine wave tracking task (Kurillo, Gregoric et al., 2005), and during a ramp tracking task (Kriz et al., 1995). Comparisons of results between tracking performance of participants with stroke in those studies and the current one are approximate only as RMSE prior to, and after tracking training, was reported graphically, and mean RMSE and variability of RMSE are not reported in the text (Kriz et al., 1995; Kurillo, Goljar et al., 2005b; Kurillo, Gregoric et al., 2005). While average RMSE, as far as can be extrapolated from the graphs provided, was similar between the previous studies and the current study at the outset, participants in the current study had a wider range of ability during the tracking tasks. Unlike the present study, most participants with stroke made large improvements in sine wave tracking with daily tracking training for four weeks (Kurillo, Gregoric et al., 2005; Kurillo et al., 2004) and ramp ascent and descent components following weekly tracking training for ten weeks (Kriz et al., 1995). It should be noted, that as in the current study, performance on an individual basis in these previous studies was highly variable; most, but not all, participants RMSE reduced after prolonged force tracking training. Prolonged peripheral nerve stimulation prior to task specific hand function training has resulted in improved grip control in participants with chronic stroke, whereas the task training alone did not (McDonnell et al., 2007). The short duration of tracking training and EMG-NMES in the current study and the variability in grip control performance of the participants may all have contributed to partial improvements in grip control only being found.

Participants in previous tracking training studies have shown the ability to transfer increases in force tracking ability learned during a training to a randomly generated signal (Kriz et al., 1995). Participants in the current study improved in the tracking task that most resembled the intervention. Training using the ramp or sine wave tasks as well may have resulted in improvements in ability to increase and decrease grip force in response to the external cues provided. In addition, as difficult tasks are more cortically demanding than simple ones, increasing the difficulty of the training task may have resulted in increases in cortical excitation (Pearce & Kidgell, 2009).

As has been previously discussed, not all people with stroke struggle with the same aspects of grip control, and some aspects may be within normal levels of performance at the outset (Blennerhassett et al., 2006a; Blennerhassett, Carey, & Matyas, 2008; Hermsdörfer et al., 2003).The mean best performance scores showed participants in the present study found the ramp descent aspect of the ramp task the most challenging of all the grip control components assessed. This is consistent with higher RMSE observed during force decrease components of tracking tasks performed by healthy controls and people with stroke (Kriz et al., 1995); suggesting a common difficulty among participants in accurately reducing grip force. It may therefore be valuable to investigate the effect of applying EMG-NMES to the finger extensors in isolation, or alternately to finger flexors and extensors, to see if altering the target muscle for stimulation would result in improvements in decreasing grip force.

The results of the current study show training specific improvements in the ramp hold aspect of the ramp tracking task. However, ramp descent, rather than ramp hold, appeared to be the most challenging aspect of the tracking tasks for these participants. If

longer duration or more intensive interventions are investigated in future, force tracking tasks could be used to identify the aspects of grip control that each participant would most benefit from training. To enable grip control interventions to be appropriately transferred to a clinical population, the association between measures of functional dexterity that are already in used clinically, such as the Box and Block Test, and aspects of grip control ability as assessed in the current study would also need to be established.

6.3.3 Grip control summary.

There was a significant improvement in grip control as shown by greater force tracking accuracy post-intervention during the ramp hold component of the ramp tracking task. There were no significant improvements in any other aspect of the tracking tasks, and no significant differences between the two interventions. Training duration, sample characteristics including age, chronicity, lesion location and baseline functional ability are all factors that may have contributed to the high variability in the data and lack of improvement in grip control in most aspects measured. A short duration intervention was able to elicit a significant improvement in grip control accuracy, and this improvement in force tracking ability was specific to the trained task.

6.3.4 Grip MVC.

Grip MVC reduced significantly following both interventions. While participants were given the same instructions and encouragement when performing grip MVC at pre- and post-intervention, it is possible that reduced motivation was a contributing factor to the decrement in grip MVC following each session. However, as there was no significant difference between the two interventions in respect of grip MVC at post-intervention, it also appears the EMG-NMES protocol was not more

fatiguing than voluntary muscle activation. In the current study, no cortical effects of peripheral muscle fatigue were found; while grip MVC significantly reduced post intervention, there was no significant change in non-conditioned MEP amplitude. MEP depression has been observed in conjunction with reduction of isometric MVC of first dorsal interosseous and proximal arm and muscles in healthy adults following electrical stimulation of those muscles (Pitcher & Miles, 2002; Todd et al., 2003). As participants in the current study were required to use sub-maximal voluntary activation of target muscles during the interventions, this may explain the difference in results between these studies. Prolonged duration interventions may have resulted in changes in cortical excitability and grip control not found in the current study, however, from these results it appears that monitoring the effect of longer duration training on muscle fatigue is advisable.

6.4 Discussion summary

Sample characteristics of age, chronicity and lack of information about lesion location are likely to have contributed to the high variability in the data found in this study. The choice of TMS methods is robust in identifying changes in cortical excitability of the lesioned hemisphere. However, changes in cortical excitability occurring adjacent or distant to the hotspot would not have been captured using this technique. As prolonged interventions may be needed to elicit or observe change in the lesioned M1, in order to more conclusively identify the immediate effects of a brief intervention, the use of mapping or other techniques to monitor cortical excitability in conjunction with paired-pulse TMS is advisable. Variability in functional and force tracking performance is likely to have affected the RMSE data. Nevertheless, a short

period of repeated force tracking training was sufficient to elicit a significant improvement in one aspect of grip control. The importance of task specificity is apparent, with improvements occurring immediately after the training session only in the test task that most resembled training. Persisting with grip control training for people with chronic stroke can therefore be recommended, but it will also be important to target participants who will get the most benefit functionally from the intervention. A number of areas for further research arise from the study in order to investigate questions raised, and maximise the improvement in grip control found as a result of the current study.

7 Further Research

A number of areas for future research have been identified in the course of this study, these include:

1. Investigating the neural and functional effects of force tracking training with and without EMG-NMES as a long duration intervention, with assessment of function in conjunction with grip control and cortical excitability outcome measures.
2. Investigating the effects of different NMES parameters on cortical excitability and function in participants with stroke, and monitoring the neural and functional effects of stimulation on antagonist non-stimulated muscles.
3. Investigating neural effects in regions other than M1 by combining neuroimaging techniques. As resource considerations may limit access to such techniques, for example fMRI, a starting point would be bilateral TMS to observe any changes that may be occurring post-intervention in the contralateral hemisphere.
4. Assessing a homogenous sample of participants in respect of lesion location, or identifying lesion location in order to assist interpretation of results.
5. Evaluating the relationship between objective measures of grip control and commonly used functional measures such as the Box and Block Test in order to screen participants or target interventions appropriately according to grip control impairments.

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Appendix A

Participant Information Sheet

Participant

Information Sheet

Date Information Sheet Produced:

7 February 2008

Project Title

The immediate changes in neural pathways and grip force control following an EMG-triggered electrical stimulation intervention in people with stroke.

An Invitation

The researchers;
Juliet Rosie, Masters Candidate and Research Officer, Health and Rehabilitation Research Centre,
Denise Taylor, PhD, Health and Rehabilitation Research Centre,
Gwyn Lewis, PhD, Health and Rehabilitation Research Centre,
invite you to participate in our study to investigate the effects on the brain and on grip control of therapeutic electrical stimulation for people who have had a stroke.
This study forms part of Juliet Rosie's Masters thesis.

What is the purpose of this research?

The brain has the potential to re organise after a stroke. Studies have shown that this potential is improved by appropriate rehabilitation. One rehabilitation tool is electrical muscle stimulation. Electrical muscle stimulation helps a muscle contract if the person has difficulty using it themselves. We are interested in finding out whether electrical muscle stimulation with active movement is a more effective tool at improving grip after a stroke than active movement by itself. We are going to be looking at the effects on the brain activity and on grip control after a half hour of therapy.
The results of this research will be published in conference and research journals.

How was I chosen for this invitation?

People who have had a stroke 6 or more months ago that has affected their hand function are invited to take part. Participation in this study is voluntary.

What will happen in this research?

You will be seated in a reclining chair for the duration of the study. Electrodes will be placed on the back and front of your forearm. Using a transcranial magnetic stimulator machine, small pulses of magnetic current will be delivered to your brain through the scalp. The pulses activate the muscles in your forearm, and the amount of electrical activity in the muscles will be measured through the electrodes. You will then perform a grip task. This involves holding a handle and following a target on a screen. To follow the target accurately you will be asked to increase or decrease the amount of force you are holding the handle with.

Once your normal brain activity and normal force tracking has been established, you will perform one of two exercises. The first will use electrical muscle stimulation to help you as you grip and release the cylinder. The second exercise is gripping and releasing the cylinder without electrical muscle stimulation. Each exercise lasts about 30 minutes.

The transcranial magnetic stimulator machine will used again to measure your brain activity immediately after the exercise and during a 10 minute rest period after the exercise has stopped. You will then do the grip force strength and tracking tasks again to see if there is any change in your ability to follow the target.

You will do four sessions; there are two testing sessions for each of the two exercises. Each session will last about an hour to an hour and a half. The sessions need to be performed on separate days at least two days apart.

What are the discomforts and risks?

Transcranial magnetic stimulation is a safe and painless procedure with negligible risks. It feels like the top of your head is being gently flicked with a fingernail. The machine issues audible 'clicks' with each stimulation, and may cause the muscles of the face to twitch as well as the muscles of the forearm. These effects stop as soon as the stimulation stops.

Electrical muscle stimulation is a safe and painless procedure. The electrical muscle stimulation causes skin under the electrodes to tingle as well as the muscles to contract. Skin abrasion required for skin preparation and heat transmitted from the electrodes may result in skin irritation and redness. These symptoms, if they occur, resolve in a few hours at most.

The manufacturers recommend that neither machine is used with people with epilepsy or pacemakers. It is also recommended that individuals with metal skull, facial or jaw implants do not have transcranial magnetic stimulation. Metal fillings in teeth are not exclusion criteria.

Volunteers who have epilepsy, pacemakers or metal skull implants will be excluded from the study.

How will these discomforts and risks be alleviated?

The level of stimulation for both the transcranial magnetic stimulator and electrical muscle stimulation will be progressively increased so that you are comfortable with the sensation. You will be asked to tell us if there is any discomfort so that we can reduce the intensity.
During each exercise there will be regular rest periods so that your arm muscles do not over-tire.

What are the benefits?

As you will only be doing four sessions of 30 minutes of exercise, long term improvements are unlikely (for those you would need to do regular ongoing exercise). We do expect to see increases in brain activity and improvements in grip force control immediately after each exercise.

What compensation is available for injury or negligence?

In the unlikely event of a physical injury as a result of your participation in this study, rehabilitation and compensation for injury by accident may be available from the Accident Compensation Corporation, providing the incident details satisfy the requirements of the law and the Corporation's regulations.

How will my privacy be protected?

Your results will be identified by a code number rather than by your name, and will be kept separate from the consent form that will have your name on it. All results and consent forms will be kept in locked cabinets. No individual will be able to be identified in any publication arising from the results.

What are the costs of participating in this research?

The cost to you of taking part is time; 1.5 hours on four days. Petrol or taxi vouchers will be provided to cover the cost of travelling to and from AUT University.

What opportunity do I have to consider this invitation?

We would like to hear back from you in 14 days. If you have any questions about this study please call Juliet Rosie on 921 9999 extension 7177 and she will be happy to answer your questions.

How do I agree to participate in this research?

If you are interested in taking part, please call Juliet Rosie on 921 9999 extension 7177. Before you can take part Juliet will need to confirm that you meet the criteria to be included. Once this is done, Juliet will arrange a time for the first session that suits you. You will need to complete a 'consent to participate' form at the first session. You are very welcome to bring your partner or support person with you if you would like them to accompany you for any of the sessions.
You will also be asked on the consent form if you want to be contacted to take part in future studies. If you agree to being contacted for future studies, your name, address and telephone number will be held on a computer database. This contact information will only be able to be accessed and used by the researchers in this study and the neurological rehabilitation team at the Health and Rehabilitation Research Centre.

Will I receive feedback on the results of this research?

Each person who takes part will receive their own results back if they want them. All participants will receive the overall results once these have been collected, no individual will be identified in those results.

What do I do if I have concerns about this research?

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisor, Denise Taylor, *denise.taylor@aut.ac.nz*, phone 921 9680
Concerns regarding the conduct of the research should be notified to the Executive Secretary, AUTEC, Madeline Banda, *madeline.banda@aut.ac.nz* , 921 9999 ext 8044.

Whom do I contact for further information about this research?

Researcher Contact Details:

Juliet Rosie: *Juliet.rosie@aut.ac.nz*, ph 921 9999 extension 7177

Project Supervisor Contact Details:

Denise Taylor: *Denise.taylor@aut.ac.nz*, ph 921 9980
Or
Gwyn Lewis: *Gwyn.lewis@aut.ac.nz*, ph 921 9999 extension 7621

Approved by the Auckland University of Technology Ethics Committee on *13 February 2008* AUTEC Reference number *08/01*

Appendix B

Participant Consent Form

Consent Form

Project title: The immediate changes in neural pathways and grip force control following an EMG-triggered electrical stimulation intervention in people with stroke.

Project Supervisors: Denise Taylor, PhD, Health and Rehabilitation Research Centre and
Gwyn Lewis, PhD, Health and Rehabilitation Research Centre

Researcher: Juliet Rosie, Masters Candidate and Research Officer, Health and Rehabilitation Research Centre

- ○ I have read and understood the information provided about this research project in the Information Sheet dated 7 February 2008
- ○ I have had an opportunity to ask questions and to have them answered.
- ○ I understand that I may withdraw myself or any information that I have provided for this project at any time prior to completion of data collection, without being disadvantaged in any way.
- ○ I do not suffer from epilepsy or any neurological condition other than stroke.
- ○ I do not have a pacemaker or any metal implants in my skull, brain or jaw (apart from tooth fillings).
- ○ I agree to take part in this research.
- ○ I wish to receive a copy of the report from the research (please tick one): Yes○ No○
- ○ I wish to be contacted about participating in future studies by the neurological rehabilitation team at the Health and Rehabilitation Research Centre.

Participant's signature:
.....
Participant's name:
.....
Participant's Contact Details (if appropriate):
……..
……..

Date:

Approved by the Auckland University of Technology Ethics Committee on 13 February 2008, AUTEC Reference number 08/01

Note: The Participant should retain a copy of this form.

Appendix C

Ethical Approval

MEMORANDUM

Auckland University of Technology Ethics Committee (AUTEC)

To: Denise Taylor
From: **Madeline Banda** Executive Secretary, AUTEC
Date: 13 February 2008
Subject: Ethics Application Number 08/01 **The immediate changes in neural pathways and grip force control following an EMG-triggered electrical stimulation intervention in people with stroke.**

Dear Denise

Thank you for providing written evidence as requested. I am pleased to advise that it satisfies the points raised by the Auckland University of Technology Ethics Committee (AUTEC) at their meeting on 21 January 2008 and that I have approved your ethics application. This delegated approval is made in accordance with section 5.3.2.3 of AUTEC's *Applying for Ethics Approval: Guidelines and Procedures* and is subject to endorsement at AUTEC's meeting on 10 March 2008.

Your ethics application is approved for a period of three years until 13 February 2011.
I advise that as part of the ethics approval process, you are required to submit the following to AUTEC:

- A brief annual progress report using form EA2, which is available online through *http://www.aut.ac.nz/about/ethics*. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 13 February 2011;
- A brief report on the status of the project using form EA3, which is available online through *http://www.aut.ac.nz/about/ethics*. This report is to be submitted either when the approval expires on 13 February 2011 or on completion of the project, whichever comes sooner;

It is a condition of approval that AUTEC is notified of any adverse events or if the research does not commence. AUTEC approval needs to be sought for any alteration to the research, including any alteration of or addition to any documents that are provided to participants. You are reminded that, as applicant, you are responsible for ensuring that research undertaken under this approval occurs within the parameters outlined in the approved application.

Please note that AUTEC grants ethical approval only. If you require management approval from an institution or organisation for your research, then you will need to make the arrangements necessary to obtain this.

When communicating with us about this application, we ask that you use the application number and study title to enable us to provide you with prompt service. Should you have any further enquiries regarding this matter, you are welcome to contact Charles Grinter, Ethics Coordinator, by email at charles.grinter@aut.ac.nz or by telephone on 921 9999 at extension 8860.
On behalf of the AUTEC and myself, I wish you success with your research and look forward to reading about it in your reports.

Yours sincerely

Madeline Banda
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: Juliet Rosie, Gwyn Lewis

Appendix D

Telephone Mini Mental State Examination

Telephone Mini Mental State Examination

Orientation:

What is the year, season, date, day, month?	Score	/5
What country, city, area, street, do you live in?	Score	/4

Registration:

Name 3 objects: *comb, pen, cup*	Score	/3
(ask person to repeat)		

Attention:

Spell "world" backwards	Score	/5

Recall:

Ask the person to recall the 3 items mentioned earlier	Score	/3

Language:

Identify the object you are speaking into	Score	/1
Repeat the following; *"no ifs, ands or buts"*	Score	/1
Say hello, tap the mouthpiece of the phone 3 times,		
and then say I'm back	Score	/3
Give a phone number where you can be reached	Score	/1
	Total score	/26

Newkirk, L. A., Kim, J. M., Thompson, J. M., Tinklenberg, J. R., Yesavage, J. A., & Taylor, J. L. (2004). Validation of a 26-point telephone version of the Mini-Mental State Examination. *J Geriatr Psychiatry Neurol, 17*(2), 81-87.

Appendix E

Transcranial Magnetic Stimulation Safety Checklist

Participant Checklist for using Transcranial Magnetic Stimulation

Volunteer Name:_____

Volunteer D.O.B.:_____ Date:_____

Has the volunteer ever been diagnosed with epilepsy or suffered from epileptic seizures?	Yes / No
Does the volunteer wear a pacemaker?	Yes / No
Does the volunteer have a metal implant in any part of their body including the head (except tooth fillings)?	Yes / No
Has the volunteer ever had a skull fracture?	Yes / No
Does the volunteer have any known skull defects?	Yes / No
Does the volunteer suffer from recurring headaches?	Yes / No
Has the volunteer suffered a head injury or concussion within the last 6 months?	Yes / No
Does the volunteer suffer from anxiety associated with medical procedures, needles etc.?	Yes / No

Checklist completed by: _____

Signature: _____