The effect of anodal transcranial direct current stimulation on spatial motor skill learning in healthy and spinal cord injured humans

A thesis submitted for the degree of Doctor of Philosophy

by

Jim Ashworth-Beaumont 0704690

School of Health Sciences and Social Care

Brunel University

September 2012

Abstract

Anodal transcranial direct current stimulation (tDCS) is an intervention which is thought to enhance motor learning in healthy and stroke-injured states, when applied adjunctively during skill learning. We set out to investigate whether anodal tDCS might enhance functional rehabilitation from incomplete tetraplegic SCI.

To address current limitations in the measurement of task-dependent skill, a novel integrated skill training and measurement task, the Motor Skill Rehabilitation Task (MSRT) was designed and developed. Measures of performance from this task delivered the functional measure of spatial motor skill learning, Task Productivity Rate (TPR). TPR was analysed and validated as a univariate dependent outcome, which is of potential importance to the future development of clinical measures measuring goal-directed motor skills.

The MSRT was included alongside conventional behavioural measures in a repeated-measures RCT pilot study, the first to investigate the effect of anodal tDCS on rehabilitation of motor skill from chronic spinal cord injury. Adjunctive application of anodal tDCS had a statistically significant benefit upon retention of skill in the incomplete spinal cord injured population, but only when the independent factor of sensory acuity was included in the analysis. Differences between the development of task-dependent skill and generic dexterity over time suggested that spatial skill development was subject to an interaction of short-term and lasting effects.

A larger study in healthy persons further investigated these phenomena, also applying Transcranial Magnetic Stimulation (TMS)–evoked measurements to investigate intervention-dependent effects upon the excitability of projections between the primary motor cortex and muscles involved in the prehension task. The findings revealed that active tDCS did not enhance skill learning at 7 days beyond the training period, but did significantly alter the development of motor skill following a period of learning and subsequent skill consolidation which was associated with underlying perturbation of motor control strategy. Significant and divergent patterns of cortical plasticity were evoked in projections to muscles necessary for reaching and grasping.

The main findings of this thesis do not support anodal tDCS as an effective adjunctive means of enhancing spatial motor skill in rehabilitation from incomplete tetraplegic SCI. If applied in patient populations, the clinical benefits of anodal tDCS may be contingent both on the nature of the sensorimotor deficit affecting upper limb function and the spatial demands of the behavioural task. The findings of this project serve to inform further research in relation to the effect of anodal tDCS on the brain and behavioural outcomes, the potential for efficacy in target patient groups and the sensitivity of outcome measures to spatial and temporal dimensions of practical motor skills.

"Seek not that the things which happen should happen as you wish; but wish the things which happen to be as they are, and you will have a tranquil flow of life."

- Epictetus ofHierapolis

"Science!"

- Dr Magnus Alfred Pyke OBE

I. Acknowledgements

Without the support and partnership of many individuals and organisations this project would not have been realised.

The Academic Supervisors, Dr Alexander Nowicky and Professor Lorraine DeSouza found the perfect balance between encouragement and constructive criticism.

Dr Angela Gall, Head Consultant, Professor Michael Craggs, Professor of Spinal Research and Iva Hauptmannova, Research and Development Manager at the London Spinal Cord Injury Centre, Royal National Orthopaedic Hospital NHS Trust provide ongoing support for patient-centred rehabilitation research. Research staff of University College London and the clinical staff of the Neuro-urology service were friends and supporters along a path which could occasionally have run more smoothly.

It was a pleasure to meet and work with each volunteer who took part in the task evaluation and research studies. The genuine interest in the research process shown by every one of those individuals served to constantly renew my enthusiasm for the topic. Particular gratitude must go to those patients who gave freely of their time and surmounted substantial physical barriers in order to take part in this research without the promise of any kind of reward.

Material support has been forthcoming from several bodies. The Brunel University Isambard Research Scholarship enabled me to sustain body and soul and also supported training and equipment costs. The Orthotist Education and Training Trust partially supported travel expenses. My employers and colleagues at the Royal National Orthopaedic Hospital NHS Trust, and in particular my Line Manager, Mr Kelvin Smith not only showed the flexibility to repeatedly modify my employment contract at very short notice but have also demonstrated active support for my academic development since 2007.

Most of all, my eternal gratitude will go to Keri, my wife and best friend for supporting me throughout every trial and tribulation over the last few years.

II. Table of Contents

III. Table of Figures

IV. List of Tables

V. List of Equations

VI. List of Abbreviations

AIS	ASIA Impairment Scale
AMT	Active Motor Threshold
ANCOVA	Analysis of Co-Variance
ANOVA	Analysis of Variance
APB	Abductor Pollicus Brevis
ASIA	American Spinal Injury Association
BB	Biceps Brachii
BDNF	Brain-Derived Neurotrophic Factor
CNS	Central Nervous System
DC	Direct Electrical Current
EEG	Electroencephalograph
EMG	Electromyograph
fMRI	Functional Magnetic Resonance Imaging
$GABA_A$	Gamma-Aminobutyric Acid (Type A)
ICF	Intracortical Facilitation
I_D	Index of Difficulty
I_P	Performance Index
JTHFT	Jebsen Taylor Hand Function Test
LTD	Long-Term Depression
LTP	Long-Term Potentiation
M1	Primary Motor Cortex
mDelt	Medial Deltoid
MEP	Motor Evoked Potential
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MSRT	Motor Skill Rehabilitation Task
MT	Motor Threshold
NHS	National Health Service
NMDA	N-Methyl-D-Aspartic Acid
NRS	Numerical Rating Scale
NT-3	Neurotrophin-3
PET	Positron Emission Tomography
PMC	Premotor Cortex
PMv	Ventral Premotor Cortex
RCT	Randomised Control Study

RMT	Resting Motor Threshold
rTMS	Repetitive Transcranial Magnetic Stimulation
S1	Primary Sensory Cortex
SCI	Spinal Cord Injury
SICI	Short Latency Intracortical Inhibition
SMA	Supplementary Motor Area
SPECT	Single Photon Emission Computed Tomography
SRc	Stimulus-Response Curve
SRTT	Serial Response Time Task
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
TPR	Task Productivity Rate
TrkB	Tyrosine Kinase Receptor B
9HPT	Nine Hole Pegboard Test

VII. Background to the Research

Introduction

Rehabilitation from spinal cord injury

Cervical-level spinal cord injury (SCI), which affects approximately half of all SCI survivors (Wyndaele and Wyndaele, 2006; Raineteau and Schwab, 2001) disrupts sensory and motor pathways. Motor control of the upper limb is impaired (Beekhuizen and Field-Fote, 2005) leading to limitations in activities and participation in the broadest sense (Kirchberger *et al.*, 2010). Tetraplegic patients value recovery of arm and hand function highly in attaining goals relating to quality of life, equal to that of bowel and bladder function (Snoek *et al.*, 2004), which makes this an important topic in rehabilitation research. Following complete SCI, improvements in functional outcome are thought due to compensation and associated motor learning alone (Curt *et al.*, 2008). But recovery of movement after incomplete SCI probably occurs via a combination of functional compensation and neuroplasticity at multiple levels (Curt *et al.*, 2008; Raineteau and Schwab, 2001).

Potential for non-invasive brain stimulation in rehabilitation

Daily dosage of tDCS during rehabilitative tasks also appears to have a cumulative effect in evoking statistically-significant, lasting improvements in functional outcomes in healthy (Reis *et al.*, 2009) Parkinsons Disease-affected (Boggio *et al.*, 2006b; Fregni *et al.*, 2006a) and stroke-affected (Boggio *et al.*, 2007) subjects compared to sham stimulation protocols, underlining the behavioural relevance of stimulation paradigms which might enhance the acquisition and carry-over of motor skills to activities of daily living (ADL) in tetraplegics (Spooren *et al.*, 2008). However, the potentially promising, practical and safe intervention of anodal transcranial direct current stimulation (tDCS) has not yet been investigated in the SCI population.

Measurement of motor skill learning in health and disease

Motor learning underlies the acquisition and improvement in performance of novel skilled movements (Korman *et al.*, 2003). Physical rehabilitation from neurological injury is concerned

with the re-learning of previously familiar motor patterns or compensatory strategies (Van Hedel and Rudhe, 2010). But in general, the mechanisms underlying the possible effects of anodal tDCS in acquiring skilled behaviour are not well understood. A weakness of clinical studies to date is that the relationship between the variables of movement time and spatial accuracy is not considered in practical outcome measures, a problem symptomatic of the basic issue that the construct of motor skill is not universally defined by researchers. Many practical motor goals involving prehension require spatial accuracy at the end-point of the movement, and it follows that outcome measures while aim to capture spatial motor skill outcomes must incorporate a metric of spatial accuracy. By extension, it is advanced that only outcome measures which capture experience-dependent changes in skill levels over time can accurately capture spatial motor learning over time.

The concept of motor learning behaviour has been investigated in depth in healthy persons and there is an existing body of literature relating motor skill to both spatial and temporal dimensions. In order to investigate the effect of an intervention upon motor skill, and any associated neuroplastic changes, we must consider the development of a skill measure capable of capturing the parameters of skilled behaviour in relation to spatial outcomes in a valid and reliable way.

Measurement of corticomotor plasticity

Neuroplasticity within the surviving central nervous system (CNS) is increasingly being understood as vital to healthy learning and the reacquisition of functional capacities lost following neurological injury, and as a means of understanding and refining the effect of therapeutic interventions (Kleim, 2011) using inferential techniques such as Transcranial Magnetic Stimulation (TMS) (Siebner and Rothwell, 2003). In animals and healthy persons, the learning of new motor skills has been associated with plastic changes in patterns of activity and excitability in the area of the brain which projects contralaterally to the muscles involved in the skilled task, known as the primary motor cortex (M1)(Monfils, Plautz and Kleim, 2005). This area of the brain is thought to play an important part in the consolidation of learned motor skills (Smyth, Summers and Garry, 2010). It has likewise been found that, in recovery from SCI lesions upper limb task-oriented training which improves the speed and accuracy of limb movement coincides with plastic increases in excitability and area of representation in M1, both in humans (Hoffman and Field-Fote, 2007; Beekhuizen and Field-Fote, 2005; Freund *et al.*, 2011) and animals (Martinez *et al.*, 2010).

TMS techniques are a practical means of investigating changes in motor connectivity in clinical studies (Devanne, Lavoie and Capaday, 1997). The short term effect of anodal tDCS on parameters of cortical excitability has been explored in some depth (Bastani and Jaberzadeh, 2012). But the lasting effect of adjunctively applied anodal tDCS on cortical excitability of M1 in relation to muscles important in upper limb functioning is little known.

Chapter 1. Literature Review

1.1 Social and functional impact of tetraplegic spinal cord injury

Worldwide, there is an annual incidence of acute traumatic SCI in the region of 15-40 cases per million (Sekhon and Fehlings, 2001) with a male to female ratio approximately 4:1 (McDonald and Sadowsky, 2002). Injury to flexible regions of the spinal column are most vulnerable to injury and therefore occur with the highest frequency in the cervical spine, which can cause the most devastating functional impairment (Ho *et al.*, 2007). Cervical-level spinal cord injury (SCI) affects approximately half (Wyndaele and Wyndaele, 2006; Raineteau and Schwab, 2001) and perhaps up to 56% (National Spinal Cord Injury Statistical Center., 2008) of all SCI survivors. Individuals suffering a lesion of the spinal cord at the level of the cervical spine will suffer impairment of upper limb motor and sensory function (Snoek *et al.* 2004) to a degree dictated by the focality of the lesion and the extent and type of sensory or motor tracts injured (Il'yasevich *et al.* 2009). Moreover, the incidence and prevalence of incomplete tetraplegia is increasing, particularly in the older age-groups (Jackson *et al.*, 2004; O'Connor, 2006; Smith, Purzner and Fehlings, 2010) as a world-wide phenomenon (van den Berg *et al.*, 2010). Over 48% of tetraplegic individuals have rated reinstatement of arm and hand function as their highest priority for functional recovery (Anderson, 2004) and in other studies stated that recovery of arm and hand function is equal to that of bowel and bladder function in attaining goals relating to quality of life (Snoek *et al.*, 2004), which highlights that functional reinstatement of upper limb function is amongst the most important topics in SCI rehabilitation research.

1.2 Neurophysiological processes associated with spinal cord injury and recovery

The most common primary mode of injury to the spinal cord in humans is via compression and contusion, whereby applied mechanical force from adjacent bodies such as the vertebrae or ligaments cause physical trauma resulting in immediate loss of function at, and below the level of the lesion (Sekhon and Fehlings, 2001; Norenberg, Smith and Marcillo, 2004). However, it seems quite rare for complete lesions to occur, and animal studies have shown that even 5% tract preservation can provide for preservation of neurological function (Kakulas, 2004).

Hence, scientific enquiry accords the search for rehabilitation strategies to maximise the potential for recovery a high priority (McDonald and Belegu, 2006).

In the hours following the acute injury, physiological changes in the environment of the cord commence with oedema and haemorrhage accompanied by cell necrosis due to membrane disruption or ischaemia, in the grey matter and also inundating the white matter of the cord (Tator and Koyanagi, 1997). The subacute phase extends between two days to two weeks following injury. During this period there is phagocytic activity (Donnelly and Popovich, 2008), peripheral astrocytes proliferate and an astrocytic scar forms which has complex functions as a chemical and physical barrier (Hagg and Oudega, 2006). In practise, the scar acts to enhance cellular homeostasis but also prevent axonal regeneration (Hagg and Oudega, 2006).

Maturation of the astrocytic scar is accompanied by regenerative axon sprouting (Hill, Beattie and Bresnahan, 2001; Coleman and Perry, 2002). In rats, endogenous adaption through sprouting of reticulospinal tracts into collaterals occurs over an extended time period (Hill, Beattie and Bresnahan, 2001). Moving into the relatively stable chronic phase beyond 6 months, all of the above processes may continue along with the formation of syrinxes or cysts, which are long-term complications as a result of altered fluid dynamics in up to a third of persons with SCI (Brodbelt and Stoodley, 2003).

1.3 Functional neuroanatomy underpinning prehension in primates

The corticospinal tracts projecting from M1 are known to be important in forming monosynaptic connections with motoneurones in primates (Lawrence and Hopkins, 1976), and particularly in relation to voluntary activity of the muscles of the upper limb (Capaday, 2004). The acquisition of skilled behaviours has been strongly linked to reorganisation of activity within M1 (Monfils, Plautz and Kleim, 2005).

The corticospinal tract is especially important for skilled upper limb function in humans, and specifically in the production of selective rather than patterned movement while other monosynaptic tracts such the rubrospinal tracts of the dorsolateral funiculus, known to carry information relevant to upper limb control are rudimentary in humans (Kanagal and Muir, 2009). These anatomical findings are borne out by further assessment of third order, intracortical connections to the monosynaptic layer V neurons which were again found to project from within the same region at levels III, II and VI (Rathelot and Strick, 2009). The feature has been found only in humans and the higher primates: In the macaque (Armand *et*

al., 1997) and the rhesus (Lawrence and Hopkins, 1976) the direct corticospinal tract develops to a great extent postnatally. The expansion of these connections increases over the time course to adulthood during which manual dexterity accordingly improves (Armand *et al.*, 1997), highlighting a dynamic co-dependence between structure and function acting throughout the CNS which subserves the achievement of behavioural goals.

A variety of studies have revealed the overlapping topography of cortical motor maps in humans (Wittenberg, 2010; Devanne *et al.*, 2006; Malcolm *et al.*, 2006) and animals (Rathelot and Strick, 2009; Rathelot and Strick, 2006; Friel, Heddings and Nudo, 2000; Nudo, Plautz and Milliken, 1997). Direct anatomical studies in macaque monkeys, which like humans are capable of highly dextrous upper limb behaviours, have assessed the distribution of monosynaptically-connected, second- and third order cortical cell representations projecting to contralateral finger and thumb muscles (Rathelot and Strick, 2009). This study found that the representations of the muscles were each all widely distributed, in overlapping distributions over the same caudal region of M1 on the anterior bank of the central sulcus, all in layer V (Rathelot and Strick, 2006). Further studies confirmed a distribution with neurons to proximal muscle motoneurone pools more medial than those of distal muscle representations (Rathelot and Strick, 2009).

Conversely in the macaque, only a small percentage of monsynaptic neurons have been found in the rostral area of the cortex on the precentral gyrus, suggesting that there is regional specialisation within M1 (Rathelot and Strick, 2009; Rathelot and Strick, 2006). In these rostral regions of M1 the layer V pyramidal neurons are mainly third order neurons, consistent with the view that neurons in this region project to interneuron disynaptic connections in the spinal cord and also to the red nucleus and brainstem (Rathelot and Strick, 2009), a feature which is found to predominate in the lower primate squirrel monkey (Nakajima *et al.*, 2000; Maier *et al.*, 1997; Lemon et al. 2004). Furthermore, comparisons between the higher primate, macaque CNS with the model of the squirrel monkey suggest that skilled distal forelimb function is directly correlated with the functionality of the direct corticomotor system to motor output and indirectly correlated with the strength of indirect propriospinal input (Nakajima *et al.*, 2000; Olivier *et al.*, 2001).

Up to 15% of monosynaptic corticomotor neurons have been found to project from area 3a of the macaque primary sensory (S1) cortex (Rathelot and Strick, 2006). This area is thought to act as an integration area for sensory information from deep receptors in skin, muscle and joints (Jones and Porter, 1980; Huffman and Krubitzer, 2001a; Heath, Hore and Phillips, 1976)

and, via the posterior parietal cortex, information coding for representations of extra-corporeal space (Medendorp *et al.*, 2008). There are also reciprocal connections with the motor nuclei of the thalamus and others suggestive of a feed-back directly from the pre-motor areas (Huffman and Krubitzer, 2001b). This suggests a direct interaction between a sensory area thought to be an important site for vestibulo-somatic integration, representational mapping and initiation of coordinated movements (Huffman and Krubitzer, 2001a) and motor output providing information important for functionally relevant adaptive behaviors such as directed reaching(Huffman and Krubitzer, 2001b).

In summary, monosynaptic projections which principally originate from the caudal regions of the primary M1 appear to be particularly important for fine motor control of the hand muscles in the higher primate (Petersen, Pyndt and Nielsen, 2003) while the disynaptic connections may be functionally more relevant to the execution of complex gross motor synergies such as reaching (Rathelot and Strick, 2006). Both of these functions are necessary for accurate prehension (Galea and Darian-Smith, 1997). But the hierarchical and heterarchical organisation of the sensory, motor and higher areas of the neocortex are complex and as yet, incompletely understood.

1.4 Evidence for effects of motor learning upon brain function in experimental animal and human models

For ethical reasons much evidence for the effects of CNS lesioning and recovery is drawn from the results of interventional experiments involving animal models and, in particular the rat strains. As a caveat, caution must be applied when extrapolating results across species with widely differing phenotypes (Manger *et al.*, 2008).

In recent years, much hope has been placed on regenerative therapies to reverse the effects of spinal cord injury, including stimulated regrowth of dorsal root ganglion neurons (Silver, 2009) and stem cell therapies (Garbossa *et al.*, 2012). However, a recent systematic review of progress in regenerative therapies concluded that there is no evidence to support the hypothesis that regenerating the lesion site is currently possible (Illis, 2011). As an alternative strategy, it has been increasingly recognised that exploitation of the innate plasticity of preserved central nervous system architecture to induce restitution of function should be a prominent area of the rehabilitation effort (Martin, 2012). Indeed, it is thought that recovery of movement after incomplete SCI probably occurs via a combination of functional compensation and neuroplasticity at multiple levels (Curt *et al.*, 2008; Raineteau and Schwab, 2001).

Learning in the motor cortex of mammals is thought to depend upon synaptic plasticity (Baraduc *et al.*, 2004; Muellbacher *et al.*, 2001). A strong determinant of synaptic strength which remodels neural network activity in learning is use-dependence (Raineteau and Schwab, 2001). Post-synaptically induced NMDA-dependent long-term potentiation (LTP) is a process thought to underlie experience-dependent synaptic plasticity (Rebola, Srikumar and Mulle, 2010) and the formation of memory (Rioult-Pedotti *et al.*, 1998). Such changes can be diminished by application of N-Methyl-D-aspartic acid (NMDA) antagonist (Butefisch *et al.*, 2000) or gamma-aminobutyric acid (GABA) agonists (Ziemann *et al.*, 2001; Butefisch *et al.*, 2000), neurotransmitters which are important in the processes of LTP (Keller, 1993) and long-term depression (LTD) (Ziemann *et al.*, 1996; Keller, 1993) respectively. In experiments involving rat subjects, GABAergic synaptic modulation appears instrumental to the disinhibition of neural networks, which signals the occurrence of rapid LTP synaptic plasticity in M1 (Jacobs and Donoghue, 1991). This mechanism has also been associated with deafferentation-induced plasticity in humans (Ziemann *et al.*, 2001).

The extent of focal excitability correlates directly with improvement in performance of motor tasks: electrophysiological study of rat preparations after specific motor skill learning uncovers plastic elevation of field potentials specific to the horizontal intracortical projections to pyramidal cells which comprise layers II and III of contralateral primary M1 (Rioult-Pedotti *et al.*, 1998). These networks may also support rapid cortical representational plasticity following injury (Huntley, 1997), processes possibly attributable to mechanisms of LTP. Rapid plastic changes are known to occur in motor cortical representation after learning which are reversed by sensory isolation from the extremities and are thought to be modulated via the intracortical connections in layers II and III (Ziemann *et al.*, 2001; Ziemann, Corwell and Cohen, 1998). In humans also, improvement in the operation of motor skills correlates with progressive M1 reorganisation (Karni *et al.*, 1998). Indeed, functional magnetic resonance imaging (fMRI) studies in humans show that mere passive joint mobilisation results in cortical reorganisation (Lotze *et al.*, 2003) an effect surpassed by active mobilisation (Perez *et al.*, 2004; Lotze *et al.*, 2003; Liepert *et al.*, 1998; Kaelin-Lang *et al.*, 2002) implying that somatosensory afferent and voluntary drive are both important factors in motor learning. Experience-dependent acquisition of novel motor skills is accompanied by rapid synaptic plasticity at the cortical level in healthy humans (Kaelin-Lang, Sawaki and Cohen, 2005; Butefisch *et al.*, 2000; Perez *et al.*, 2004) and also in primates following SCI (Schmidlin *et al.*, 2004).

Intermediate processes have been identified which may be instrumental in learning, but could also explain the effects of anodal tDCS on motor learning. The BDNF protein is a known regulator of cell survival, proliferation and synaptic growth in the CNS as well as a modulator of NMDA-dependent LTP (Leßmann and Brigadski, 2009). BDNF is known to be released both pre- and post-synaptically (Kuczewski, Porcher and Gaiarsa, 2010) from neurons by synaptic activity within the CNS, is present in high levels in the pyramidal cells of the hippocampus and neocortex (Yan *et al.*, 1997)and acts as a messenger for structural and functional change (Gottmann, Mittmann and Lessmann, 2009). The secretion of endogenous BDNF (thought to be secreted post-synaptically via the dendrites in cortical pyramidal neurons (Lessmann, Gottmann and Malcangio, 2003; Kuczewski, Porcher and Gaiarsa, 2010) has been shown to be bidirectionally dependent upon tDCS-induced brain polarisation (Antal *et al.*, 2010).

The receptor type Tyrosine Kinase Receptor B (TrkB) encodes a receptor for several neurotrophins but has the greatest affinity for BDNF (Squinto *et al.*, 1991). The binding of BNDF to TrkB receptors is known to activate intracellular cascades associated with processes including LTP and synaptic plasticity associated with the formation of motor and spatial

memories (Yamada and Nabeshima, 2004; Mizuno *et al.*, 2003). Changes in BDNF levels at the level of M1 may also help to induce changes remotely, at the level of the spinal cord. In an in vivo experimental rat model of the spinal cord post-incomplete injury, infusion of BDNF adjacent to the cell bodies of descending pyramidal neurons in M1, or Neurotrophin-3 (NT-3) to the spinal cord of Lewis rats showed that, while NT-3 infusion increased collateral fibre density post-injury, only cortical infusion of BDNF resulted in a significant association between functional improvement on a ladder walking task and increased collateral sprouting and bouton termination onto proprioceptive interneurons and other, surviving corticospinal tracts at the cervical level of the spinal cord (Vavrek *et al.*, 2006). The study is of particular interest because it demonstrated that structural plasticity around the lesion site may not be necessary for functional recovery to take place. On the contrary, exogenous facilitation of synaptic plasticity in M1 via increases in extracellular BDNF levels can not only enhance synaptic plasticity locally but may also be associated with remote structural and behavioural plasticity that can be related to improvements in sensorimotor function (Vavrek *et al.*, 2006).

Partial recovery of manual dexterity may be effected by optimisation of information transmission via surviving direct corticospinal projections (Galea and Darian-Smith, 1997), or functional compensation via adaptive remodelling of more complex, stereotypical motor patterns (Kanagal and Muir, 2009). Both processes may require extensive neuroplasticity at the cortical level (Schmidlin *et al.*, 2004). Recent TMS studies including human cervical SCI patients versus healthy controls has shown the shift of M1 cortical excitability maps of functionally active forearm muscles controlling the wrist into the area previously occupied by the denervated hand muscle representations. The study also found that the extent of spinal cord atrophy, measured using Magnetic Resonance Imaging (MRI), was associated with reduction in corticomotor excitability and transmission latency to the hand muscle (Freund *et al.*, 2011), illustrating the adaption of cortical connectivity in compensation for denervation to support behavioural adaption in humans, which has been observed in detail in the higher primate (Nishimura and Isa, 2009).

Likewise, in experimentally-induced C2 incomplete SCI rat subjects, the repetitive practise of a reaching task in the acute phase led to the restoration of cortical maps along with significantly enhanced skills learning (Girgis *et al.*, 2007; Krajacic *et al.*, 2009). Acute-phase rat subjects significantly resorted to compensatory movement in an untrained task, suggesting limited generalisation of the trained skill which perhaps relates either to the acute plasticity of cortical maps (Girgis *et al.*, 2007). On the other hand, rats trained 16 days after lesioning experienced

significant skills learning without resorting to compensation, suggesting that delayed rehabilitation is more beneficial. Furthermore, in the chronic subjects no expansion of cortical mapping was observed suggesting that cortical map expansion in the acute subjects may have been related to maladaptive plasticity affecting non-trained performance (Girgis *et al.*, 2007) while trained task improvement in both groups indicates that map expansion may not be a requirement for skills learning (Krajacic *et al.*, 2009). Taken together, these results raise a question over whether, in the chronic *human* SCI condition the learning of a specific skill is more widely generalisable, or conversely whether early training in a specific task could actually impair performance of untrained tasks.

In the human, altered focal excitability and area of representation correlate with the level of functional impairment in SCI, hence constituting maladaptive plasticity (Bruehlmeier *et al.*, 1998; Green *et al.*, 1998; Cohen *et al.*, 1991; Topka *et al.*, 1991; Jurkiewicz *et al.*, 2007). But following SCI, the extent of cortical activity area relative to healthy persons correlates with the level of functional recovery (Jurkiewicz *et al.*, 2007). Longitudinal cortical mapping studies of thenar and elbow flexor muscles following acute cervical spinal cord injury found early expansion of the preserved biceps representation (Streletz *et al.*, 1995) and other surviving representations (Schmidlin *et al.*, 2004). In experimentally spinally-injured rats, use-dependent recovery of tactile sensitivity (or forced use) and the extent of forepaw cortical representation are interdependent, with the rapid recovery of sensory function likely to occur via the spinothalamic tract (Martinez *et al.*, 2009). This highlights the importance of normal function of the sensory dorsal columns in sensorimotor control, lesioned as part of this study. At the same time, the recovery of sensory function was associated with spontaneous plasticity of intraspinal networks ipsilaterally, decussating below the level of injury. It is thought that collateral sensory neurons may have been unmasked as a form of synaptic plasticity, ascending within surviving spinothalamic tract and synapsing at the thalamus to maintain the pre-existing somatotopic representation at S1 (Martinez *et al.*, 2009). However, in the main these studies support the notion that following spinal cord injury in mammals, limited regeneration occurs both above and below the level of the injury and that functional improvement is associated with adaption of the surviving CNS (Bareyre *et al.*, 2004).

Such findings highlight the critical importance of this level of the neuraxis in aspects of motor learning for recovery from neurological injury. In fact, experience-dependence, sensitivity to intervention exposure time, behavioural motivation and attention in driving CNS plasticity seem to transcend clinical speciality and are ubiquitous themes in conservative, activity-based

approaches to treatment (Cramer *et al.*, 2011). Short-term interventions such as anodal tDCS, which may have an additional beneficial effect upon learned motor behaviours in the long-term (Reis *et al.*, 2009) may yet prove to be powerful modulators of functional recovery in rehabilitation from SCI in humans.

1.5 Modulation of brain and behavioural functions with Non-invasive Brain Stimulation (NIBS) modalities

Non-invasive brain stimulation (NIBS) modalities are increasingly considered as possible interventions to alter the excitability of cortical regions underlying the area stimulated, and thereby temporarily modify motor outcomes in both health and disease (Bolognini, Pascual-Leone and Fregni, 2009). Repetitive TMS (rTMS) (Reis *et al.*, 2008; Conte *et al.*, 2008; Edwards, Talelli and Rothwell, 2008) and transcranial direct current stimulation (tDCS) (Nitsche *et al.*, 2005; Rosenkranz *et al.*, 2000; Reis *et al.*, 2009; Tanaka *et al.*, 2009) as two forms of NIBS are currently of clinical interest and with comparable behavioural effects, though the underlying mechanisms might be quite different. Current evidence suggests that these techniques may be capable of producing clinically beneficial effects upon skilled motor behaviour, which has encouraged continuing avenues of research in both healthy states and patient groups, supported by ongoing studies in vivo and vitro animal models (Paulus, 2011).

In humans, the benefits of non-invasive brain stimulation (NIBS) as potential forms of treatment include relative non-invasiveness, focality of effects and the association with mild side-effects, in comparison to oral pharmacological intervention for example (Williams, Imamura and Fregni, 2009). Barker et al. first described the technique used in Transcranial Magnetic Stimulation (Barker, Jalinous and Freeston, 1985). In its' modern form, tDCS has been understood as a means of modulating cortical excitability in the human brain for more than a decade (Nitsche and Paulus, 2001; Nitsche and Paulus, 2000; Nitsche *et al.*, 2008). tDCS is regarded as a relatively safe NIBS modality as shown by animal experimentation (Liebetanz *et al.*, 2009) and the outcomes of numerous studies in humans (Brunoni *et al.*, 2011; Bikson, Datta and Elwassif, 2009) although symptoms of pain and minor skin burns have been associated with excessive current density (Furubayashi *et al.*, 2008) and variance in application technique (Frank *et al.*, 2010; Palm *et al.*, 2008) respectively.

1.5.1 Basic mechanisms and stimulation parameters underpinning the effects of NIBS modalities

The basic mechanism of action of rTMS is underpinned by Faraday's Law: by rapidly varying the intensity of a magnetic field produced by an appropriately constructed and oriented coil antenna placed onto the scalp overlying the brain area of interest, electrical currents can be induced trans-cranially in horizontally-oriented neurons close to the surface of the skull which may then result in neurotransmitter release at their terminal synapses (Priori, Hallett and Rothwell, 2009). The effect of this stimulation is dependent upon the intensity, number and frequency of induced stimuli, where low frequency (≤1Hz) and high frequency (≥5Hz) application result in respective reduction and increase of cortical excitability which can last beyond the duration of the stimulation (Pascual-Leone *et al.*, 1999). Thus, rTMS is therefore considered to be both a neurostimulatory and neuromodulatory intervention (Williams, Imamura and Fregni, 2009). More complex patterns of stimuli, such as theta burst stimulation (TBS) which mimics observed patterns of brain activity, increases the potency of rTMS frequencies and so reduces the stimulator intensity and number of stimuli required to induce effects (Huang *et al.*, 2005; Huang and Rothwell, 2004). However, for the same reason the potential for inducement of seizures is present using rTMS paradigms and increased by TBS (Oberman and Pascual-Leone, 2009) which limits clinical application without careful risk assessment of participant populations (Rossi *et al.*, 2009; Wassermann, 1998).

While tDCS does not directly induce action potentials, it is thought that changes in the level of polarisation by several mV will alter the level of discharge of neurons (Priori, Hallett and Rothwell, 2009). This NIBS modality is applied through application of weak direct electrical currents (DC) to the scalp via electrode pads. DC currents are applied to the scalp via electrodes during tDCS stimulation, using safety-approved devices. The effects of tDCS are principally dependent upon current amplitude and polarity, whereby the 'active' electrode is that which is placed on the scalp over the target region of the brain, physical size of electrode placement and duration of stimulation (Williams, Imamura and Fregni, 2009; Paulus, 2011). Some studies utilise accurate placement techniques based upon MRI or TMS measurements of the area of greatest response from the cortical muscle representation (Hummel *et al.*, 2010; Hunter *et al.*, 2009; Hummel *et al.*, 2005). Others have used the arbitrary positions C3 and C4 of the 10-20 EEG system (Klem *et al.*, 1999) for the placement of tDCS electrode pads over the M1 region of interest (Hesse *et al.*, 2011; Vines, Cerruti and Schlaug, 2008; Hesse *et al.*, 2007; Fregni *et al.*, 2006b).

The area of the electrode pad and the size of the applied DC current together give rise to a current density parameter which is thought to be an important determinant of the electric field strength (Nitsche *et al.*, 2008) producing a steady-state extracellular field which in turn gives rise to the effects of tDCS (Bikson *et al.*, 2004). Therefore, the current density is important in producing the effect size (Paulus, 2011). However, the static electrical field is thought to be produced by the small amount of current flow not shunted via the skull and cranial tissues, modulating the membrane potentials of neurons underneath the target area of the cortex (Paulus, 2011). There is limited evidence to show that increases in current density has a proportional effect upon MEP excitability (Nitsche and Paulus, 2000) but the effect of varying current density on behavioural outcomes is not known.

The effects of tDCS depend both on the placement of the electrodes upon the scalp (Section VII.1.9) and the polarity of application: early animal experimentation showed that, while cathodal tDCS has a hyperpolarising effect anodal tDCS depolarised cortical neurons (Purpura and McMurtry, 1965) modifying the spontaneous discharge rate of corticomotor neurons respectively downwards and upwards (Gartside, 1968; Nitsche and Paulus, 2000). Specifically for investigation of the effect of anodal tDCS upon motor performance, it is routine to place the anode onto the scalp overlying the M1 region of the cortex contralateral to the performing limb and with the cathode placed on the opposite supraorbital region (Nitsche *et al.*, 2008). Findings suggesting that anodal tDCS in particular can enhance the retention of motor memory in a lasting fashion may be dependent upon the plasticity of cortical networks involved in the encoding of memory.

Studies on in vitro preparations of rat cortex have shown that neuronal morphology correlated with the extent of polarisation such that layer V pyramidal neurons were optimally polarised due to their orientation to the field (Radman *et al.*, 2007). Action potential threshold reduction correlated with cell polarisation and synaptic network activation with layer V/VI neurons oriented with the gradient of the electrical field more sensitive to polarisation than layer II/III neurons, the effect of which was to up-regulate action potential firing times and promote burst firing (Radman *et al.*, 2009) with other studies indicating effects upon neuronal afferents suggestive of plasticity of 'upstream' network function (Bikson *et al.*, 2004).

Post-synaptically induced NMDA-dependent long-term potentiation (LTP) is a key mechanism in formation of experience-dependent synaptic plasticity (Rebola, Srikumar and Mulle, 2010) upon which depend the effects both of rTMS (Huang *et al.*, 2007) and tDCS (Nitsche *et al.*, 2003). It has been known for some time that glutamatergic NMDA receptors appear to exhibit

temporal dependency on membrane voltage by which action potentials arise at depolarisation (Morris, 1989; Morris *et al.*, 1986). Applying anodal tDCS using established protocols (Nitsche *et al.*, 2008) temporarily increases focal corticospinal excitability (Nitsche *et al.*, 2005) and appears to be directly associated with changes in functional connectivity in the human brain (Polanía *et al.*, 2011) a phenomenon otherwise occurring subsequent to selective voluntary activity and associated with the consolidation of motor memory (Rioult-Pedotti *et al.*, 1998; Lotze *et al.*, 2003; Nitsche *et al.*, 2003). Furthermore, anodal tDCS-induced LTP is abolished in BDNF- and Tyrosine Kinase Receptor B (TrkB) receptor- knockout mice (Fritsch *et al.*, 2010). Therefore, akin to those processes involved in experience-dependent plasticity, anodal tDCS may modulate activity-dependent synaptic plasticity dependent upon mechanisms driven by endogenous BDNF secretion and TrkB activation (Fritsch *et al.*, 2010).

1.5.2 Effects of NIBS modalities upon motor behaviour in animals and human subjects

The action of tDCS modalities on specific neural circuits may be task-dependent. Following experimental lesioning of M1 in rats (Kim *et al.*, 2010) anodal tDCS improved uptake of motor skills in the acute recovery phase associated with improvement in the myelination of axons within the internal capsule. However, no change in the physical dimensions of the lesion was found over this period, suggesting either that secondary facilitation of glial (oligodendrocyte) activity is a factor in the anodal tDCS induced augmentation of motor performance (Kim *et al.*, 2010) or at least that processes related to upregulation of corticospinal activity may drive the differential presence of myelin sheath due to the intervention.

In humans, concurrent application of anodal tDCS to the contralateral M1 area enhanced the cortical activity normally associated with phasic joint movements during a task (Kwon and Jang, 2011). Furthermore, anodal tDCS has also recently been associated with a modulatory effect on interneuron activity at the cervical (Roche *et al.*, 2009) and lumbar spinal level (Roche *et al.,* 2011), providing further evidence that brain stimulation modalities could have a plastic effect upon the activity of distributed neuronal networks both up and downstream from the stimulation site. This appears to be a feasible hypothesis because spike-timing dependent plasticity has previously been driven at the spinal level by temporally associating TMS single pulses with antidromic peripheral stimulation, to vary evoked EMG and force output bidirectionally (Taylor and Martin, 2009). This is of interest because patients exhibiting spasticity demonstrate relative loss of disynaptic inhibition compared to those with normal

tone or flaccid paralysis (Nakashima *et al.*, 1989) suggesting that anodal tDCS application enhances at least short lasting disynaptic inhibition by modification of spinal network excitability (Roche *et al.*, 2009) which might be achieved by enhancement of corticospinal tract activity. Perhaps modification of the spontaneous discharge rate observed in animal (Purpura and McMurtry, 1965) and humans (Nitsche and Paulus, 2000) can, via intermediate mechanisms induce increased plasticity of networks at the spinal level.

The artificial augmentation of neuroplastic processes by non-invasive means may be useful for functional rehabilitation from disease, by enhancing the naturally-occurring processes of plasticity underlying performance and learning (Sadowski, 2008). At the level of behaviour in humans, both rTMS and tDCS methodologies have been explored experimentally in a range of participant groups. Sham-controlled studies focusing on motor control have assessed the effect of either increasing the excitability of the affected hemisphere using either anodal tDCS (Boggio *et al.*, 2007; Hummel *et al.*, 2006; Fregni *et al.*, 2005a; Hummel *et al.*, 2005) or high frequency rTMS (Khedr *et al.*, 2009; Kim *et al.*, 2009), or inhibiting the activity of the unaffected hemisphere using cathodal tDCS or low frequency rTMS (Khedr *et al.*, 2009; Kirton *et al.*, 2008; Takeuchi *et al.*, 2008; Liepert, Zittel and Weiller, 2007). The majority of these studies have looked at short term, transient effects only although Boggio and colleagues (2007) and Fregni and colleagues (2006) have respectively considered the effect of repeated tDCS and rTMS applications upon the consolidation of lasting motor memory, with positive behavioural outcomes demonstrated (Fregni *et al.*, 2006c; Boggio *et al.*, 2007).

1.6 Temporal effects of tDCS upon the brain and motor behaviour

Application of either tDCS polarity for several minutes induces effects which can last beyond the period of application (Bolognini, Pascual-Leone and Fregni, 2009). In order to achieve plastic after-effects upon cortical excitability beyond the period of stimulation, as indicated by the size of motor evoked potentials (MEP), it has proven necessary to apply tDCS for at least three minutes with a currect of 0.6mA or more (Nitsche and Paulus, 2000). Within limits the duration of stimulation appears to dictate the period of altered excitability. Following 9 minutes of cathodal tDCS stimulation MEP sizes were reduced for 60 minutes (Nitsche *et al.*, 2003), while more than 5 minutes (Nitsche and Paulus, 2000) and up to 13 minutes of anodal tDCS stimulation caused excitability to be increased for up to 90 minutes (Nitsche and Paulus, 2001; Monte-Silva *et al.*, 2012). Standardised dosage with anodal tDCS with duration of 20 minutes resulted in sustained MEP increases and enhancement of motor function in

Parkinson's disease patients (Fregni *et al.*, 2006a). A number of further behavioural studies in healthy persons and patients have established that 20 minutes anodal tDCS dosage improved motor outcomes (Boggio *et al.*, 2006a; Boggio *et al.*, 2006b; Hummel *et al.*, 2010; Fregni *et al.*, 2005a). But 26 minutes of continuous anodal tDCS resulted in lasting inhibition of MEPs (Monte-Silva *et al.*, 2012), an homeostatic effect which might be regulated by activity-dependent intraneuronal calcium concentration (Misonou *et al.*, 2004).

1.7 Evidence for efficacy of anodal tDCS on motor functions in humans

Previous studies on complex motor tasks in healthy individuals (Sohn, Kim and Song, 2012; Hummel *et al.*, 2010; Boggio *et al.*, 2006a) and patient groups (Bolognini *et al.*, 2011; Kim *et al.*, 2009; Hummel *et al.*, 2005) highlight the benefits of anodal tDCS to elicit positive short-term effects on motor performance. These studies involve pre-training in a validated task to a stable state, followed by application of anodal tDCS at an intensity of 1 to 1.5mA and then re-measuring following the stimulation intervention to determine changes in motor function (Figure 1.1). The task utilised in most such studies investigating this intervention is the Jebsen Taylor Hand Function Battery (JTHFT). This functional test battery captures the metric of completion time in standardised tasks, which together test the ability to utilise a range of grasp and strength patterns (van Tuijl, Janssen-Potten and Seelen, 2002). Kim and colleagues utilised the Box and Block Test, a simpler prehension test utilising objects of a standardised size (Yancosek and Howell, 2009). The metric of choice in general is completion time, which is inferential of net movement rate.

Serial Response Time Task (SRTT) paradigms involve the implicit learning of a motor sequence, with the output usually applied mechanically via a keyboard using the fingers. This type of task has been adopted as an outcome measure in experimental psychological studies investigating influences upon implicit motor learning (Robertson, 2007). Anodal tDCS has also been shown to have a lasting positive effect on reaction times in SRTT-based paradigms (Kang and Paik, 2011; Nitsche *et al.*, 2003). A further study looked at the effect of anodal tDCS on the short-term enhancement of task consolidation i.e. continued improvement in a task following the end of training (Krakauer and Shadmehr, 2006), of a pre-learned SRTT-like task (Tecchio *et al.*, 2010). The significantly reduced completion time in the trained SRTT task sequence was attributed to strengthening of trained cortical networks (Tecchio *et al.*, 2010).

Stagg and colleagues found that application of anodal tDCS dosage during an explicit sequence learning task led to an ongoing enhancement of reaction times compared to sham or cathodal tDCS conditions – the latter condition has been shown to supress the excitability of M1 (Stagg *et al.*, 2011). But the application of anodal tDCS prior to the learning period had a negative, slowing effect on reaction times. The authors attribute this disassociation of effects to a homeostatic mechanism acting upon motor learning based upon the order of stimulation and training.

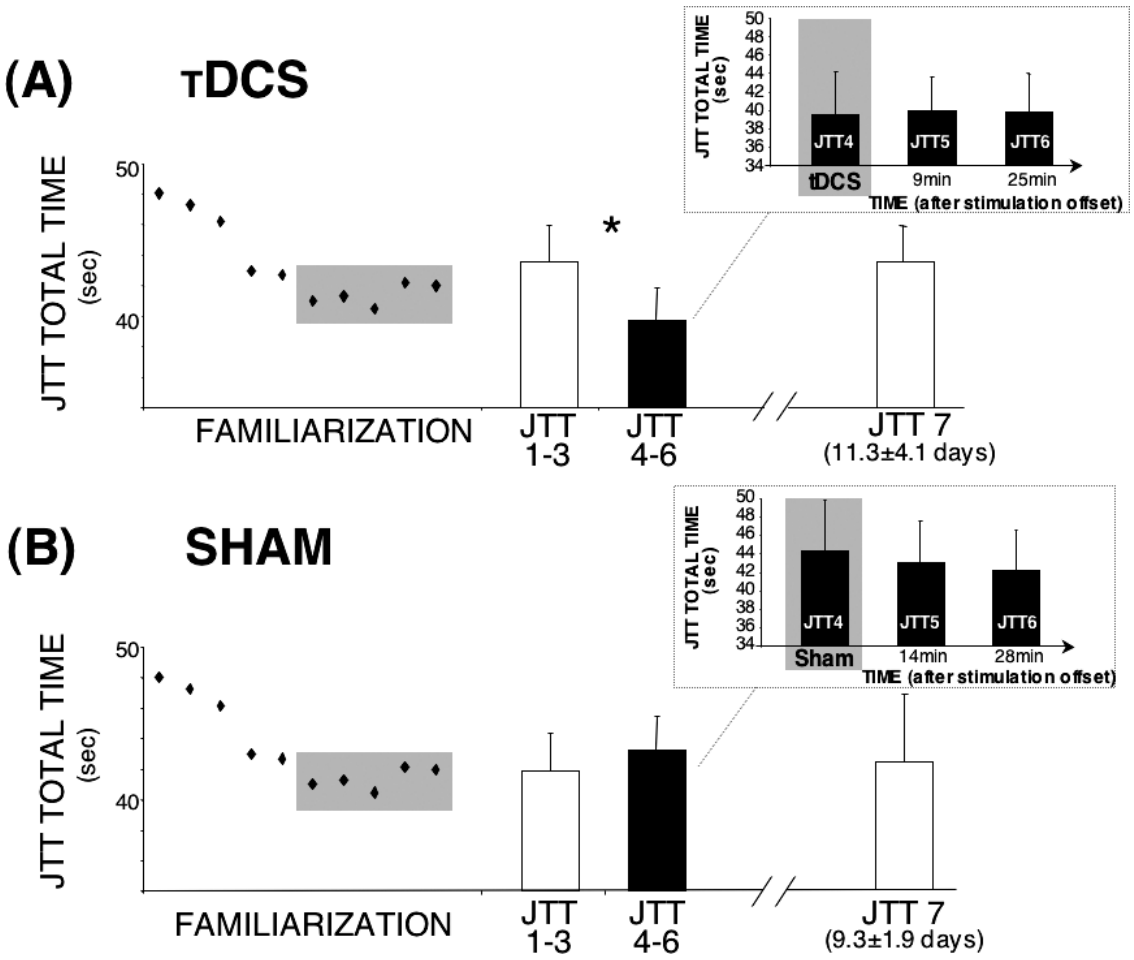


Figure 1.1: Typical study design format for experimental tDCS study.

The behavioural task (JTT - Jebsen Taylor Hand Function Test) is trained to a stable state prior to taking of a baseline. Completion time is the metric evaluated. The experimental effect is evaluated as the between-groups difference between active (A) and sham control (B) intervention states, in relative change between baseline and post-intervention task practise scores.From Hummel et al., 2005.

One behavioural study presented evidence of long-term enhancements in outcomes 3 months after training with adjunctive anodal tDCS. This novel task paradigm applied a range of guided movement rates dependent upon the mechanical activation of a single degree-of-motion mechanical pinch force interface, with the environment of the virtual task featured a positive force field. Improvements in motor skill were inferred from shifts in the log-linear gradient of the speed/accuracy trade-off during repetitions of a standardised sequential task, demonstrating significant enhancements of the speed/accuracy tradeoff over measurement intervals extending up to 3 months from the intervention period (Reis *et al.*, 2009).

A number of studies have documented the short-term effect of anodal tDCS on maximally voluntary contracted strength in the lower and upper limbs (Tanaka *et al.*, 2011; Hummel *et al.*, 2006)and endurance (Cogiamanian *et al.*, 2007) with the further finding that anodal tDCS may have the capacity to modify the time-course of adaption to resistive artificial force-fields (Hunter *et al.*, 2009) and the learning-dependent change in simple joint kinematics through a combination of motor practise and adjunctive stimulation (Galea and Celnik, 2009).

Taken together, the above evidence suggests that anodal tDCS has a possible utility in enhancing physical parameters and outcomes inferential of motor skill. However, the evidence available to date can only be said to provide evidence of improvements in the temporal skill parameter, with the associated effect upon spatial accuracy left unknown (VII.1.8.1). Because motor skill is fundamentally defined by the interaction of spatial accuracy with movement rate, it must be stated that there are issues with the dimensions captured by, and interpretation of the outcome measures applied in previous studies.

Though a number of studies have highlighted the beneficial effect of this intervention on motor performance, the behavioural results in respect of complex motor outcomes are by no means uniformly positive. Bastani's systematic review of included studies established a large but non-significant effect size in healthy persons (Bastani and Jaberzadeh, 2012). Furthermore, a small and non-significant effect was found in stroke-affected subjects (Bastani and Jaberzadeh, 2012). Stagg et al. found behavioural improvements on response times in chronic stroke patients where M1 was spared (Stagg *et al.*, 2012). But chronic stroke patients with mixed lesions did not benefit from robotic gait-retraining where anodal tDCS was applied adjunctively compared to the sham condition (Geroin *et al.*, 2011). Likewise, adjunctive tDCS modalities had no effect of the response to robotically-assisted bilateral upper limb training in chronic stroke patients with cortical injuries (Hesse *et al.*, 2011). However, a cross-over study

showed that lower limb muscle control was improved in a cohort of chronic stroke patients with mild impairment and spared M1 (Madhavan, Weber II and Stinear, 2011).

Subacute stoke patients might also benefit from this intervention: finger acceleration and Box and Block Test were improved for 60 minutes post-intervention compared to a sham control condition (Kim *et al.*, 2009). Subcortical stroke-affected chronic patients also improved in terms of reaction time and pinch force (Hummel *et al.*, 2006) and the JTHFT complex motor task (Hummel *et al.*, 2005). Furthermore, in a cross-over study, 4 patients with sub-cortical stroke derived lasting benefit from repeated training over 4 weekly sessions (Boggio *et al.*, 2007). But 50 acute stroke patients with mixed lesions derived no lasting benefit from anodal tDCS in a matched groups, RCT format when activity and deficit were assessed at 5 days and 3 months following a 5-day intervention (Rossi *et al.*, 2012), hinting that the clinical outcome measures applied in previous studies do not accurately reflect the requirements of activities necessary for functional independence.

There may be a greater clinical benefit for individuals with relatively greater deficits. More severely involve stroke patients appeared to derive more benefit (Hummel *et al.*, 2006) while the greater the age of the individual, the proportionally better were the outcomes (Hummel *et al.*, 2010).

The general observations on the above evidence are that, to date, there is limited evidence of either short term or lasting benefit in motor learning in patients. Significant enhancements in motor function appear to be contingent on an intact M1 and the selection of simple outcome measures which do not critically examine the accuracy of task end-points. In the absence of co-morbid injuries, the architecture of the brain is fully preserved in tetraplegic SCI patients and and so we might expect to see a clearer beneficial effect of anodal tDCS on motor skill learning if it exists. Furthermore, this neurologically-impaired population may be a useful group to study, where the relative effects on motor learning and motor performance may be disassociated from other factors for heterogeneity that might be associated with stroke injury (Ones *et al.*, 2009) such as variable damage to brain centres.

1.8 Motor learning

1.8.1 A critique of current approaches to measurement of goal-based behavioural outcomes

This critique is limited to that range of current clinical measures identified which seek to infer levels of sensorimotor function from the result of a goal-based metric, at the International Classification of Function and Disability level of Activity (Cieza and Stucki, 2008) and with regard to unilateral upper limb function. Exemplars are discussed.

Many objective measures of motor skill are available to assess the level of upper limb manual dexterity or motor skill, in both patients and healthy persons. All those considered simulate some series of practical dextrous motor behaviour which broadly involves the repetitive enactment of several tasks which take place over the following phases of prehension: grasping and manipulation of an object, aiming towards a target of some sort during which grasp might require adaption to the target profile, object placement and release (Elliott *et al.*, 2004). Finally, the end effector (the hand) is returned to the start position to start a further repetition of the task.

Single-task clinical measures of manual performance aim to achieve high measurement precision in a particular construct by focusing on limited repetitions of single tasks composed of several identical elements. Examples of this class of measure are the 9-hole peg test (9HPT) (Oxford Grice *et al.*, 2003) or the Grooved Pegboard Test (Bryden, Roy and Spence, 2007). This type of test can suffer from floor effects through an intolerance of spatial error, whereby the validity of the task result is compromised if it is not completed without error within a practical time limit. An alternative approach is to measure how many times a standardised subtask can be completed over a limited time period: the Purdue Peg Test (Buddenberg and Davis, 2000) falls into this category. Again, success depends on completing subtasks successfully and the difficulty of the task is mitigated by the design of the target as a socket on a flat board, so that a peg can be manoeuvred across a board surface and into the target, by a process of trial and error if necessary.

By these means the issue of error recording is avoided, but by the same rationale construct validity in terms of a precise reflection of practical motor performance is limited. Ceiling effects in these procedural tasks occur where a subgroup of individuals find the tested procedure sufficiently easy that improvement in the dependent variable (usually completion time) is no longer sensitive to the independent variable of interest. Floor and ceiling effects

both act to reduce the target spectrum of applicability, because the occurrence of errors during the enactment of the measurement task reduces the validity of the measure.

In the effort to encompass a wider functional spectrum and/or range of abilities some instruments apply a battery of different sub-tests to measure different aspects of motor function to capture a variety of skill domains. These may then be aggregated or summarised in some way to give an overall score. The issue here is that, precisely because a number of attributes are measured simultaneously, by definition it is difficult to implement task batteries as training and measurement tasks for investigating specific task-dependent motor skill and learning effects. The Jebsen Taylor Hand Function Test (JTHFT) (Jebsen *et al.*, 1969) is a prominent and long-standing example of the class, being first intended as a clinical assessment of several aspects of arm/hand function and is widely used in experimental research where it is commonly used as training task and an inferential measure of task-dependent motor skill state in healthy persons and patient groups.

The issue of motor skill measurement is particularly prominent in the field of neurorehabilitation research where the effect of central nervous system injuries is highly variable between survivors. In order to avoid the introduction of bias from use of an insensitive instrument, investigator restrict study inclusion criteria to participants who are considered homogenous for the construct being measured, within the psychometric range of linearity for that measure of the dependent variable (Yancosek and Howell, 2009). The ideal characteristics of a motor skill instrument therefore include wide-spectrum applicability – the task should be accessible to those with profound motor impairment but also be capable of sensitively detecting motor skill levels up to the elite skill level in healthy persons.

Though it has long been recognised that spatial accuracy of movement is an essential parameter of skilled manual performance, there is as yet no universally-accepted means of defining spatial-temporal performance within a measurement interval. The measurement dimension of the current measurement instruments discussed is chiefly that of completion time, because it can be easily evaluated using simple equipment. There may occasionally be some attempt to evaluate spatial errors (Hummel *et al.*, 2010). However, though the challenge is well-understood, no successful and practical solutions to the quantitative definition of motor skill in terms of completion time and end-point accuracy have been offered. In general, we submit that because spatial error is not measured as an integral dimension of task performance in any current accepted tests there may therefore be limited relevance to the construct of motor skill of which completion time is only one attribute.

There has been an attempt to resolve the issue, by integrating the spatial and temporal parameters into a univariate skill measure. The work of Reis and colleagues (Reis *et al.*, 2009) which investigated the lasting effect of anodal tDCS on skilled performance in healthy persons provided valuable insights into the issues surrounding objective measurement of motor skill. Variables were gathered from a single spatial dimension computer-based serial reciprocal movement based task, utilising a hand pinch grip force interface. For this study, the researchers developed and utilised a skill measure based upon a logarithmic transformation of an empirically-derived speed*error/accuracy function, and with skill parameter *a* (Equation 1.8-1). The results revealed improvements in skill due to anodal tDCS lasting up to 6 months past the training period.

$$a = \frac{\text{1-error rate}}{\text{error rate } (\ln(\text{task duration})^{\text{b}})}$$

Equation 1.8-1: Function for the skill parameter *a* (Reis et al., 2009)

But in deriving the skill measure several potential flaws were introduced. Apart from a number of mathematical assumptions made about the stability of individual 'non-skill' parameters over time, it was reasoned by the researchers that accurate estimates of the relationship between target error/accuracy and movement rate could be found from separately averaged proportional number of trials in which 1 or more errors occurred and task durations over a given sample of training trials. It is argued that as this was of limited validity a mathematical approach, because the assumption was made that the distribution of both parameters remained stable over time, which was not proven. Furthermore, the expression included terms representing both spatial error and spatial accuracy (the '1-error rate' term). The rationale for the approach taken is unclear, but the practical effect of applying this function to the derivation of a skill measure appears to multiply the effects of reducing errors and increasing movement rate upon the skill outcome. We reach this conclusion because, as shown in Equation 1.8-1, while the essential parameter of spatial skill is spatial accuracy, spatial error is widely predicted to increase proportionally with movement rate in movement to spatial targets. This factor alone may have resulted in the reported increasing level of mathematical noise over time, which prompted the application of a further logarithmic transformation (Reis *et al.*, 2009). Despite the best efforts of the researchers to accurately evaluate both spatial and temporal dimensions of motor skill (Reis *et al.*, 2009), the reported improvements in the skill

measure could have been due either to inaccuracy in the model rather than improvements in motor skill.

Finally, although the outcome measure employs dimensional limits for the quantification of performance errors, this being an abstract task it is difficult to estimate the stringency of the error constraint on behaviour. This is important because motor control, as the effective balance between movement and spatial accuracy, and the learning of motor skill is thought to depend respectively upon observation of spatial variability in spatially demanding skilful tasks (Guigon, Baraduc and Desmurget, 2008) and integration into future movement plans (Novick and Vaadia, 2011; van Beers, 2009). This, it is argued, is the basis of a flaw in all existing clinical measures of motor dexterity: if the tolerance constraints of targets are not stringent than the measure may not be sensitive to increases in spatial variability.

In summary, while spatial variability is an explicit dimension of all practical, skilled goal-oriented movements, none of the validated surrogate measures (Roland and Torgerson, 1998) discussed carry information about success in achieving spatial end-points and so are not capable of integrating spatial and temporal dimensions. These measures cannot therefore represent the construct of practical motor skill as we have chosen to define it. It is this limitation which gives rise to issues with the sensitivity and linearity of current clinical measures: spatial goal errors, occurring due to high spatial variability in target aiming, result in floor effects while highly accurate aiming capability results in ceiling effects (Barak and Duncan, 2006) compromising the generalizability of experimental results to clinical outcomes (Roland and Torgerson, 1998).

1.8.2 Factors in uptake and retention of motor skills

The phenomenon of long-term motor skills retention appears to depend firstly upon the extent of repetition priming, specifically training of a specific set of task items beyond performance saturation during a training session rather than direct correlation with the extent of repetition (Hauptmann and Karni, 2002). 'Off-line' (between sessions) improvements in skill, might occur, for example, following over the day following practise or over a subsequent period of sleep (Debas *et al.*, 2010; Gomez Beldarrain *et al.*, 2008; Karni and Sagi, 1993). This process of consolidation of the motor memory might rely on the stabilisation of the performance improvement in motor circuits (Karni *et al.*, 1998). fMRI Imaging studies have identified that consolidation of motor adaptation tasks is time-dependent either during the daytime or sleep and is correlated with activity in the posterior parietal cortex and cerebellum, but motor sequence learning is strongly sleep dependent with neural activation in the striatum and contralateral primary M1 (Debas *et al.*, 2010). Likewise, disruption of the primary M1 with rTMS following blocked-practise motor training protocols impaired performance of the skill but without impairing sleep-induced enhancements, suggesting that respectively different mechanisms for motor performance and memory retrieval may be responsible (Robertson, Press and Pascual-Leone, 2005).

A further and perhaps related factor to be considered is the effect of similar interference tasks which interact negatively upon the priming effect of the first task (Hauptmann and Karni, 2002). Blocked repetition of motor tasks is thought to result in better improvement in speed and accuracy of execution than those motor skills, although the reverse appears to be the case when retention over time and transfer of the skill over time is concerned (Lee, Swanson and Hall, 1991). This effect is thought to be due to the greater contextual interference when going through random practise, requiring greater cognitive demands and thus allowing for greater flexibility when integrating the learned patterns into action plans (Li and Wright, 2000).

Training load or dosage might be an important time-dependent component of the degree to which motor training persists as a skill. Ghilardi and colleagues examined the relative contribution of explicit and implicit components to the process of learning a sequential motor skill (Ghilardi *et al.*, 2009), and the interference effect of learning a second sequence upon the first. Training with the second sequence interfered significantly with implicit performance when this took place 5 minutes after training with the first, but no interference was found if the second sequence was trained 24 hours after the first. Conversely, explicit recall of first sequence order was impaired even when interference training was applied a full 24 hours

after. However, exposure to increased training load of either the first or second sequence protected against interference with the learning process of both suggesting that embedding of the implicit components of movement kinematics occurs as a process separate to the explitic learning of movement sequence (Ghilardi *et al.*, 2009).

The detection and interpretation of error signal-to-noise ratio around an optimal outcome is a vital component which enables task tuning to maintain an acceptable level of control, and the prevention of consequences that are considered to be negative (Amalberti, 2001). But it has also been found that, with increasing expertise knowledge-based errors decrease while routine-based errors increase, where the error rate is maintained at a level sufficient to maintain a satisfactory level of control via implicit mechanisms (Valot and Amalberti, 1992). Indeed, laboratory-based studies have shown that introducing uncertainty to the location of a target in a reaching task results in the implementation of more variable joint movement strategies (de Freitas, Scholz and Stehman, 2007) suggesting firstly that, as found by Ghilardi et al. (Ghilardi *et al.*, 2009) motor planning is a necessary part of fluent movement but also that non-task based training to improve implicit movement accuracy may be of some benefit in addressing problems of adaption to similar but novel activities of daily living. This would be detected in an experimental study as an intervention-dependent improvement over time in a similar but non-trained task.

Studies in primates demonstrate the exponential reduction in the spatial variability of movement trajectories with practise as the main determinant factor in skill improvement in aimed tasks (Georgopoulos, Kalaska and Massey, 1981). This finding has recently been repeated in humans, and thought to be driven mainly by changes in motor and sensory representations that increase the neural signal-to-noise, as distinct from the model-based mechanisms in cerebellum that quickly reduce systematic sources of error (Shmuelof, Krakauer and Mazzoni, 2012). Studies in healthy participants suggest that there is a relatively greater improvement in successful adaption to variations in more complex object interception tasks (leading to decreased error, or improving skill level) when the task is first practised in a simplified format - that is, that use of redundant solutions in motor tasks may be emergent from learning of a task-relevant parameter (Ranganathan and Newell, 2010a). In other words, improving the ability to carry out a critical element of the complex movement task – such as refinement of shoulder kinematics, for example – may be key to the successful utilisation of later redundant movement solutions. Therefore, we might postulate that the repetitive practise of critical elements in a reaching movement may be transferable to skill levels in other

tasks – at least those tasks which serve a similar behavioural outcome. Simplified interpretation of kinematic errors in particular, as shown to be important in previous studies (Scheidt *et al.*, 2000; Shadmehr and Mussa-Ivaldi, 1994) might enhance the speed of development of internal dynamic model development within the CNS, within the limited context of the motor task type implemented in the present study.

In studies of adjustment to external perturbations, TMS and tDCS have both been used as an intervention to assess the role of M1 in this aspect of motor learning, by brain stimulation before, after or during a learning task. Pre-interventional practise of motor task to plateau level in repeated-measures designed studies have revealed short term enhancements of performance (error or speed) by facilitatory or inhibitory interventions such as anodal tDCS or cathodal tDCS respectively. Additionally, the comparison of different stimulation methods can provide clues as to the function of specific brain areas. For example, 1Hz rTMS applied to M1 did not impair short-term adaption to a robot-induced dynamic force-field (Baraduc *et al.*, 2004), but anodal tDCS applied during the adaption phase increased de-adaption time (Hunter *et al.*, 2009). These results suggest that anodal tDCS may enhance the rate of development of an internal force model (Hunter *et al.*, 2009). If this is the case, M1 itself may be important as part of a distributed network in adaption to different ballistic conditions (Baraduc *et al.*, 2004).

1.8.3 Joint kinematics and learning effects in prehension

Muscles which feature prominently in grasping, hand orientation and reaching are the deltoids (shoulder abduction and medial rotation) (Fujiwara *et al.*, 1999), brachioradialis (elbow flexion and secondary wrist pronation (Boland, Spigelman and Uhl, 2008)) extensor carpii radialis for wrist extension and tenodesis grip and the thenar muscles for thumb opposition (Brochier *et al.*, 2004).The inclusion of a limited repertoire of time-varying motor synergies has been shown in the execution of wide range of functional activities in the limbs of healthy animal models (Bizzi *et al.*, 2008) and the shoulder and elbow of healthy humans (d'Avella *et al.*, 2006). Individuals implement basic hand shapes with fine tuning of finger posture to achieve adaptive grip exists both in healthy (Mason, Gomez and Ebner, 2001)and C6/C7 SCI subjects, despite the motor deficit in the latter group (Jacquier-Bret, Rezzoug and Gorce, 2008). Grasp implementation is object-specific and repeatable, though differing somewhat between individuals, both in humans (Wong and Whishaw, 2004) and other mammals (Brochier *et al.*, 2004).

Observations of reaching actions have shown that healthy human reaching is characterised by optimisation of sub-movements in the approach to a reaching target, most commonly in initial under-reaching (Meyer *et al.*, 1988) and this succession of under-reaching movements even after training gives rise to a sustainable means of addressing prevailing sources of random error in the most energy conservative way (Elliott, Hansen and Grierson, 2009). These findings provide a sound basis for the implementation of complementary targeting mechanisms for accurate reaching - an internal forward model, which is optimised for systematic variations in environmental parameters (Burge, Ernst and Banks, 2008) with the ongoing requirement for ongoing monitoring of spatial error during the reaching action (Medina, Jax and Coslett, 2009) which can respond to environmental perturbations at latencies of less than 200ms (Saunders and Knill, 2005). In fact, in combination these mechanisms might provide the functional basis for an inherently flexible motor system consistent with the theory of motor abundance (Latash, 2012) with the capacity to continue systematic searching for the optimal kinematic strategy under steady state external environmental conditions (Ranganathan and Newell, 2010b).

Accurate control of the end effector is thought to depend both on a balance between forward modelling in movement planning (Churchland, Afshar and Shenoy, 2006) and correction via real-time information in the approach to the target (Proteau *et al.*, 1987; Todorov, 2004). Constant visuomotor feedback, vital for control in the approach to the target requires response latencies greater than around 160ms to have an effect upon the outcome (Saunders and Knill, 2003) and recent kinematic findings suggests that the optimal corrective movement must occur early in the timecourse of successful reaching movement (Kwon, Shelton and Chiu, 2009).

Maintenance of performance over both distance and direction (i.e. accuracy) does appear to be conditional upon the maintenance of available visual feedback throughout the entirety of the movement (Saunders and Knill, 2005; Saunders and Knill, 2003; Proteau *et al.*, 1987). But smooth shaping of the hand during the approach to object grasping is contingent in part upon intact mechanoreception in the fingers (Monzée, Lamarre and Smith, 2003) rather than continuous visual feedback (Winges, Weber and Santello, 2003). The necessity for parallel sensorimotor pathways to mediate fine manual dexterity have been shown in primates where, even in the absence of motor impairment, experimental reduction in the distribution or richness of mixed afferent feedback impacts negatively upon the accuracy of feedforward motor output (Darian-Smith, Burman and Darian-Smith, 1999). Dependent on the relative

impact of sensory and motor deficits in incomplete tetraplegia, the combination of these problems might reduce the abundance of possible movement synergies normally found in healthy individuals during upper limb function (de Freitas, Scholz and Stehman, 2007; Robertson and Miall, 1997), forcing the implementation of alternative, individually variable gross motion strategies to achieve the desired objective (Galloway and Koshland, 2002).

The reach system appears to construct an accurate model based on the task-dependent transformation of somatosensory information (Monaco *et al.*, 2010), which in turn provides for the optimal use of multiple sensory modalities in action planning (Brenner and Smeets, 2011). Following injury to the spinal cord there is a reduced capacity for parallel information processing and increased reliance upon serial processing in spared tracts (Darian-Smith, Burman and Darian-Smith, 1999). The presence of spared yet demyelinated or dysmyelinated long tract axons is thought to be a common feature in functionally incomplete SCI (McDonald and Belegu, 2006) as shown in animal models (Radojicic *et al.*, 2005; Nashmi and Fehlings, 2001) and post-mortem in humans (Guest, Hiester and Bunge, 2005; Bunge *et al.*, 1993) a process which may actually progress over time post- SCI (Totoiu and Keirstead, 2005).

This might have two independent effects upon motor performance. While limb kinematics in reaching are broadly preserved despite profound paralysis of important muscles (Hoffmann *et al.*, 2006), when sensory input is impaired there is reduced potential to improve the spatial precision of the forward model, through ongoing comparison of expected with actual outcomes based on sensory information (Otten, 2005). Therefore the degree of sensory preservation might be expected to directly impact on the rate of motor learning.

1.8.4 Theories underlying goal-directed aiming in prehension

In 1899, Woodworth first posited that a relationship between speed and accuracy existed during rapid aiming tasks, and depended upon central, feedforward and feedback-mediated mechanisms (Elliott, Chua and Helsen, 2001). According to this model initial, ballistic movements bring the extremity towards the target area at which point feedback mechanisms are initiated to guide the movement to a successful conclusion. Slower movements were considered to provide for more feedback-driven correction to take place, resulting in an inversely proportional relationship between accuracy and the parameters of movement amplitude and speed (Elliott, Chua and Helsen, 2001).

Fitts and colleagues used an experimental approach to investigate the capacity of the human motor system which itself includes indivisible visual, proprioceptive and cutaneo-sensory

components (Fitts, 1954). It is useful to discuss this important work as it outlines the concepts used to justify analysis of the motor task data in the present project. The experimental designs, utilised 4 different tasks requiring hand dexterity and limb reaching movements, controlled for task amplitude and limits of tolerance, and subjects were instructed to work with the emphasis on accuracy. The researchers postulated that the work rate would be limited by the information processing capacity required to complete the task with an acceptable level of accuracy, in a motor system containing a fixed level of noise as a source of motor error.

From the data, a non-linear (logarithmic) mathematical relationship was defined between the physical parameters of the task (mean movement amplitude *A*, target width *W*) as an index of task difficult (I_d) (Equation 1.8-2).

$$I_D=-\log_2\frac{W}{2A}\,bitspertrial.$$

Equation 1.8-2: Index of Difficulty (I_D) for a standardised spatial target (Fitts, 1954).

I_D is directly proportional to target width *W* and indirectly proportional to amplitude of the reaching movement *A*.

Note that this relationship is applicable to repetitive tasks by multiples of movement amplitude *A* where *A* is taken to be the normally-distributed mean of all possible amplitudes (Fitts, 1954), thus may be applied to net performance in more complex tasks, and the information carrying capacity required to complete the task successfully over *n* trials increased proportional to the task I_d. From Equation 1.8-2 a performance rate index (I_p) could be derived, with I_p as the expression of information transfer rate (Equation 1.8-3).

$$I_p = -\frac{1}{t}\log_2\frac{W}{2A}\ bits/second.$$

Equation 1.8-3: Performance Index (IP) of information carrying capacity in relation to a standardised target (Fitts, 1954).

I_P is directly proportional to target width *W* and indirectly proportional to amplitude of the reaching movement amplitude *A* and duration of the movement time *t*.

It was found that, although each task had a different I_D, I_p remained fairly constant over a limited range of varied task parameters with the most consistent performance associated with movement amplitudes of between 4 and 8 inches (roughly 10 and 20cm respectively). It was postulated that the healthy human motor system does indeed have a limit of performance defined by the capacity to process sensory monitoring of movements within the physical parameters of the task, which may be generalizable to all physical tasks (Fitts, 1954). However, the information carrying capacity of the hand may, by virtue of the compound movements of individual fingers be higher than that of the arm (Fitts, 1954) and so conversely we should consider the possibility that neurological impairment of the hand might have a relatively more profound effect on the performance of complex dexterity tasks.

In a subsequent work, Fitts and Radford expanded these findings and varied the cognitive approach (speed-emphasis, accuracy-emphasis or self-selected cognitive approaches) under which subjects carried out motor skill tasks. They again found evidence to show that, although reductions in movement time (due to increasing movement speed) resulted in increases in task error, the information carrying capacity of the human motor system appeared quite constant under different cognitive sets (Fitts and Radford, 1966).

Keele's review of movement control (Keele, 1968) observed that successive repetitions of movement result in a shift from feedback mediation to increasing integration of movements into (feed-forward) motor programs, providing a practise-dependent model for the time-

dependent development of motor memory in skilled tasks. In simple terms, the Keele model suggested that feedforward motor programs are refined with practise and explains the persistence of longer completion times in difficult tasks within an iterative model, where successive correctional movements in closing to an aiming target are ballistic in nature and require multiple separate learned motor programs rather than being feedback-driven (Keele, 1968). Others have suggested that the speed-accuracy relationship is not related to feedback and increased levels of error creep in because of the increasing muscular and inertial forces acting over the period of the task, which then give rise to the increased variability of end-accuracy placement (Schmidt *et al.*, 1979), but this is the case only for the fastest movements when visual feedback is availiable (Schmidt *et al.*, 1979).

Conversely, akin to Woodworth's model the intermittent feedback model posited by Beggs and Howarth (Beggs and Howarth, 1972) advanced that the speed-accuracy relationship in reaching to a task is a function of the approach trajectory and the accuracy of the early ballistic phase as well as the inherent variability due to systemic noise. Based on earlier research, correction of ballistic errors was thought to take place at a fixed time (290ms) before the termination of successful task trials (Beggs and Howarth, 1970). Using a metronome to guide movements at different speeds in a reach-to-target task, utilising right-handed subjects in blocks of 20 trials, where illumination was broken at different distances from the target, the researchers empirically demonstrated that at given speeds the target error depended upon the distance from target at which the last correction was applied. Furthermore, increasing the speed of the movement increased the distance from target at which the corrective movement needed to take place in order to make an accurate placement (Beggs and Howarth, 1972), providing support for the experimental hypothesis.

A more sophisticated model explaining Fitts' explanation of the speed-accuracy tradeoff and the variability of movements near to targets suggested a ballistic, feed-forward movement phase followed by an optional corrective phase (Meyer *et al.*, 1988). This model made an assumption that the combined optimisation of these movements would result from an optimal performance to minimise average movement time and error rate, the results of which are stochastic due to the inherently noisiness found in biological sensorimotor neural networks. Empirically, this research group found that the variation in end placement position around a target centre follows a normal distribution (as expected in a sensorimotor system subject to noise) and that the variation grows linearly with the velocity of the movement (Meyer *et al.*,

1988). Error rates also increased with target difficulty, even in the trained condition, thought to provide evidence against the iterative Keele model (Meyer *et al.*, 1988).

In accordance with this model, termed the stochastic optimised-submovement model, the variability of fast movements is greater and therefore requires more corrective movements in order to achieve the target area. The overall target time approach selected by participants must determine the maximum speed of the primary ballistic movement but with minimal need for one or more corrections in the face of the interent noisiness of the system, which is a practise-dependent process. Optimal trials will minimise the number of corrections required and thus maximise the mean performance over successive trials.

The form of the trade-off characteristic between movement rate and spatial accuracy may depend upon the demands of the experimental task – hence, theoretical models may be limited. The linear trade-off relationships found between temporally-constrained movement tasks (linear) are thought to be compounded by the additional factor of spatial constraints to give rise to the logarithmic relationship found by Fitts and in many physical tasks (Meyer *et al.*, 1988). Thus, Fitts's law may have general applicability in motor performance. The latter type of task parameter, free of temporal constraint is thought to allow more readily for the optimisation of movements to develop in a practise-dependent fashion. However, Meyer's data also indicated that, following training, subjects do not consistently produce optimal movement patterns, suggesting that the subjective perception of target difficulty gave rise to variability in the cognitive approach resulting in less and more corrective submovements being applied to easy and difficult targets respectively. This variability in initial cognitive approach, combined with the variability due to noise in the sensorimotor system, may tend to give rise to greater variability in the performance outcome though it remains to be seen whether this variability in approach improves average performance compared to temporally-constrained trials with fixed spatial constraint. It may be important to at least limit the cognitive approach via instructions in order to standardise cognitive approaches to the task (MacKenzie and Isokoski, 2008) and limit performance extremes (Platz, 2004).

In the acquisition of improved control in tasks involving redundant degrees of freedom, a large number of redundant degrees of freedom may give rise to the same result. Inter-trial variability in kinematic pathways may persist independently of reductions in end-point variability which accompanies improvements in task skill (Müller and Sternad, 2009). Indeed, others have found that spatial variability mid-path was always greater than the variability at the target, indicating that subjects continued to utilise redundancy in describing the kinematic

pathway toward the spatial goal (Ranganathan and Newell, 2010b). A practical benefit of this trajectory variability may be innate flexibility in dealing with changes to the task complexity, such as intermediate obstacles in three-dimensional and two-dimensional tasks (Vaughan *et al.*, 2010; Jax, Rosenbaum and Vaughan, 2007). A parsimonious interpretation of the stochastic model suggests that open-loop models tend towards optimisation of accuracy and energy consumption, but in the presence of a noise level which is proportional to the speed and amplitude of the task effort which requires intervention with closed-loop feedback control (Todorov, 2004). Again, this theory is consistent with Fitts's law: high speed open-loop motor commands driving early submovements incur greater trajectory error, thus must end earlier in order to accommodate closed-loop secondary corrective movements. In such a state the acceleration profile is skewed towards the earlier part of the movement to achieve successful target matching with the behavioural goal. However, optimal controllers seem to offer minimal intervention, so that energy expenditure is utilised only when on-line error is likely to affect the goal.

Similarly, in a reciprocating task, movement speed was faster after placement within target area, but slowed down when the target was missed and gradually recovered after several correct trials independent of task difficulty, as dictated by target size (Brenner and Smeets, 2011). Furthermore, individuals tended to increase speed over the primary reaching phase rather than the terminal end-point phase of reaching suggesting that the requirement for corrective submovements close to the target were anticipated regardless of the history of success, and were shown not to be due to a reduction in variability. This provides evidence that end-point variability depends on the speed of movement near the endpoint, rather than a reduction in motor noise. Near-optimal performance can develop quickly in very short period of time and is reactive to a limited number of prior trials, without the need to learn the extent of task-dependent motor variability (Brenner and Smeets, 2011).

To summarise, various models have been developed which place different emphasis on feed-forward and feed-back driven behavioural mechanisms in speed and accuracy parameters. These models, which appear to be applicable to such diverse activities such as sequential and reciprocal reaching, wrist rotation and finger movements do not, however encompass the time dependent changes in goal-dependent aiming behaviour which occur with practise due to learning.

A further question which arises is if, and if so how, short term mechanisms are associated with the longer-term mechanisms of motor learning? That is, does modifying the parameters of motor practise modulate the extent of plasticity, and hence the extent of refinement in motor skill? Does practise of a given motor skill result in the consolidation of feedback-reliance towards an open-loop, feedforward motor program? This implies the development of a motor program, or succession of motor programs as postulated by others (Keele, 1968; Schmidt *et al.*, 1979).

A strategic approach tends to develop in which a balance between end-point variability, speed and energy expenditure is reached (Elliott, Hansen and Grierson, 2009). In tasks where the target is of a fixed size, early submovements will fall outside of the target footprint in a relatively large number of trials compared to performance after practise, thus the number of trials in which one or more corrective submovements via a process of visually-controlled limb-target fixation and fine adjustment of limb kinematics late in the movement is required will be large during early practise and progressively smaller as the level of skill improves (Starkes, Helsen and Elliott, 2002; Binsted *et al.*, 2001). Error can approach but never reach zero due to the stochastic, noisy nature of the human motor system. Indeed, rather than embedding motor sequences into open loop programs it seems that that skill may develop by virtue of improving the processing efficiency of sensory information via some sort of comparator mechanism (Schmidt *et al.*, 1979).

There is a body of recent work, revisiting the work of Fitts and Radford which itself elaborated the theory that the human motor system, in totality and including sensory pathways has a limited and invariant capacity for throughput (successful execution) of a skilled task (Fitts, 1992). The throughput might be dependent upon two competing factors, speed and accuracy of task completion, in an environment where the amplitude of movements is relatively fixed. They further showed, utilising a reciprocal manual aiming task that, where the amplitude of movements was fixed this 'trade-off' persisted independent of the 'cognitive set' – that is, subjects demonstrated an upper limit to throughput no matter whether they were asked to emphasise speed or accuracy of execution, or move at a self-selected rate (Fitts and Radford, 1966). Mackenzie and colleagues empirically demonstrated that Fitts' theory on constant throughput was upheld independently of significant reciprocal changes in completion time and accuracy, along with the expected observation that variability of placement position is more erratic at high execution speeds (MacKenzie and Isokoski, 2008).

Guiard and colleagues clarify the empirical phenomenon in more general terms including the constants of task geometry, target distance and tolerance which incidentally are fixed properties in the MSRT task utilised in the present project. These authors further discuss the throughput constant, represented by the quantity 'q', in terms of the maximal investment of resources by an individual or population sample, each of whom possesses a limited-resource pool at a given time (Guiard, Olafsdottir and Perrault, 2011). Where the environmental parameters relating to the task are stable, the speed accuracy trade-off is redefined in terms of movement time and relative error, the latter variable defined by the statistic of movement error against movement amplitude (Guiard, Olafsdottir and Perrault, 2011).

1.8.5 Co-regulation of movement time and spatial error in skill measurement

Simmons and colleagues investigated the skilled behaviour of 16 children with foetal alcohol spectrum (FAS) compared to age-matched healthy controls in a classic Fitts' reciprocation task to targets using a computerised interface (Simmons *et al.*, 2011). FAS is associated with structural anomalies in the CNS and behavioural and intellectual impairments (Riley and McGee, 2005) but also deficits in visuomotor integration and fine motor skills (Mattson *et al.*, 1998) affecting the velocity timing of target-oriented movements (Wass *et al.*, 2002). The important finding of this study in the current context is that, though the researchers found that both healthy and pathological groups produced skilled outcomes according to a linear Fitt's Law function relating movement rate and target difficulty, and closely matched skill based upon indexes of performance I_P, the pathological FAS group were only able to achieve this by increasing movement rates to compensate for a significantly higher net spatial error rate (Simmons *et al.*, 2011), but also suggesting that motor control and learning is governed to maximise I_P. Likewise, a similar study in 32 children with developmental coordination disorder and learning disability (DCD-LD) compared to controls found that significantly more errors occurred during performance of cyclic motor tasks between fixed points and were associated with faster end-point velocities that appear compensatory in nature (Smits-Engelsman *et al.*, 2003). Both of these studies suggest that increased movement rates can be a viable strategy to maintain information transfer rates in compensating for innate deficits in spatial accuracy (Simmons *et al.*, 2011; Smits-Engelsman *et al.*, 2003) albeit a more energetic strategy.

By testing the effects of applying loads to the arms of DCD children, it was ascertained that the pattern of behaviour towards increased movement rates was driven by the impairment of

open-loop, or feed-forward modelling because the children had difficulty in integrating the force and timing components of movements (Wilson *et al.*, 2001) which would lead to a discrepancy between the expected and actual reaching endpoints. The authors suggested that the pattern of behaviour was associated with a greater reliance on direct stimulus-response feedback of innate deficits in spatial targeting and a reduced ability to develop the limited strategy (Smits-Engelsman *et al.*, 2003) towards the learned, action-dependent, predictive open-loop internal models required for motor optimisation (Novick and Vaadia, 2011). But equally, the outcomes on I_P, which were approximately equal to the result from healthy controls, indicate that the pathological groups achieved motor skill levels (as we also currently define it: Section VII.1.11) equal to the healthy groups over the period of these observational studies. The generalizable inference is that individuals who are subject to greater levels of net spatial error may be able to *implicitly* apply effective alternate systematic strategies to maintain motor skill at healthy norm levels.

This strategy involving increased movement times might be a signature of compensation for sensorimotor impairments limiting prehension end-point accuracy to fixed targets, because healthy subjects are known to reduce peak velocities as reaching tasks increase in difficulty (Park, 2002) under self-guided movement rates, all other task variables being equal (Park and Kim, 2008). In fact, in healthy persons this kinetic and kinematic refinement in upper limb functionality is a viable strategy for the preservation of goal success in fatigued states (Missenard, Mottet and Perrey, 2009)}, perhaps because reductions in movement rate allow more time for address the effects of random motor noise upon reaching actions (van Beers, 2009).

Likewise, in adults affected by cerebral palsy, subjects performed a Fitts' law task with a high degree of error but significant usage of ballistic movement to achieve the aim of the task, reaching to targets of varying difficulty, though the researchers were unable to establish a significant 'Fitts' log-linear association between movement time and the difficulty of the targets: perhaps this was due to the heterogeneity of the sample (Gump, LeGare and Hunt, 2002). Thus, effective co-regulation of motor output with observations of spatial error is thought to be important for both motor performance and motor learning (Novick and Vaadia, 2011) but relative defects of visuo-motor processing might be inferred from the strategy employed in reaching tasks.

1.8.6 Training and measurement of task-dependent skill

Large dosage repetitive task-specific training of manual tasks over time-limited intervals has been shown to promote plastic changes in neural representation (Girgis *et al.*, 2007; Nudo *et al.*, 1996; Karni, 1996) and generalise to validated scales of upper limb function in improving functional ability in chronic neurological impairment (Birkenmeier, Prager and Lang, 2010). Furthermore, the literature suggests that the intervention of interest, tDCS is of benefit in improving function in a lasting fashion when applied adjunctively to complex motor tasks in healthy (Reis *et al.*, 2009) and neurologically impaired (Boggio *et al.*, 2007) populations. Conversely, research in animal models of tetraplegic SCI suggest that the neuroplasticity and functional improvement associated with task-dependent training may not generalise out to untrained tasks, and in humans short-term adaption to changing force environments was significantly altered to modify de-adaption following application of anodal tDCS (Hunter *et al.*, 2009).

Block training in standardised tasks over limited periods of time is thought to offer effective results in rehabilitation (Birkenmeier, Prager and Lang, 2010). In rehabilitation from stroke, a modular form of activity training known as Arm Ability Training (AAT) implements motor tasks intended to address specific aspects of impairment in motor control including movement speed, aiming and dexterity (Platz, 2004). In contrast to methodological concepts based on massed therapy and individualised treatment strategies, in this paradigm the work load, consisting of standardised tasks, is limited by the baseline capability of the participant. Variation of goal difficulty in the task is applied which is thought to enhance motor learning. The task instructions call for the therapist to encourage speed of the activity without compromising accuracy in the goal.

Compared to conventional modes of therapy the AAT protocol was shown to produce significantly better results for both for short-term and lasting benefits, suggesting that this type of standardised and highly structured form of training has relevance for efficacious carry-over to activities of daily living (Platz, 2004). Knowledge of results, though thought to be important for explicit motivational purposes, does not seem to have an effect upon the outcomes of long-term studies showing efficacy at a year post-training compared to conventional methods (Platz *et al.*, 2001). Likewise, the outcomes were not significantly sensitive to psychological factors which might constitute biases, such as depression and cognitive factors such as attentional ability (Platz and Denzler, 2002).

1.9 Rationale for stimulation of M1 to induce changes in motor performance

Where the aim of tDCS application is to influence the performance of skilled motor activity, tDCS modalities have most commonly been applied with the active electrode overlying the M1 region of interest. It is well-established that the degree of local cortical excitation of M1, as elicited by TMS-evoked measures, is dependent upon the duration and intensity of the applied direct electrical current (Nitsche and Paulus, 2000). In fact, it was found that significant corticomotor excitability changes following tDCS stimulation only took place when the active electrode was placed over the target area of M1 and the reference electrode placed over the contralateral forehead (Nitsche and Paulus, 2000). Though the premotor regions also have access to the spinal cord via direct connections (Dum and Strick, 1991) and in general are known to be important for on-line planning and of hand and arm movements (Buch *et al.*, 2010; Kantak *et al.*, 2012; Platz *et al.*, 2012a) M1 is highly interconnected with other motor regions in both cortical hemispheres, as well as the cerebellum, parietal and sensory areas and is therefore thought to act as an integrative centre for diverse influences on motor behaviour (Reis *et al.*, 2008).

There is an evidence-base for considering M1 as an area particularly important for procedural motor learning (Sanes, 2003). During, and in the hours following motor skills training, improvements in ability which can persist for years are accompanied temporally by changes in the pattern of representation in M1 areas projecting to muscles involved in the task (Karni *et al.*, 1998). Changes in the excitability of M1 projections specific to target muscles involved in a skilled ballistic task were found to be temporarily increased following training (Muellbacher *et al.*, 2001). It was further demonstrated that application of rTMS to M1 shortly following motor practise could attenuate retention of a learned of a motor skill (Robertson, Press and Pascual-Leone, 2005; Muellbacher *et al.*, 2002), whereas control stimulation of the prefrontal or occipital cortices had no effect (Muellbacher *et al.*, 2002). These findings suggest that a critical process takes place in M1 over 1 or 2 hours following skilled performance during waking hours (Robertson, Press and Pascual-Leone, 2005; Muellbacher *et al.*, 2002) which is necessary for the acquisition and retention of the skill (Robertson, Press and Pascual-Leone, 2005). Hence, by influencing the excitability of M1 it may be possible to modulate the efficacy of motor learning processes, which could have useful applications in rehabilitation (Priori, Hallett and Rothwell, 2009).

M1 is known to be particularly active in the inter-trial interval during practise of skilled motor tasks (Lin *et al.*, 2010) suggesting a learning process subserving the laying down of lasting motor memories involved in subsequent skilled performance (Monfils, Plautz and Kleim, 2005). In the non-dominant upper limb, following prolonged skill training protocol, performance was not contingent upon activity of M1, the primary S1, the premotor cortex or the sensorimotor associative area (Platz *et al.*, 2012b). In contrast, after a period of training from the naïve state, S1 was important for motor performance and learning, whereas activity in M1 region was specifically engaged during enactment of rapid movements (Platz *et al.*, 2012a). This association between structure and function in the brain suggests that M1 is concerned with reproduction of learned motor engrams rather than direct skill learning. Likewise, the excitability of M1 was increased significantly 24 hours after, but not immediately following learning of a manual skill (Smyth, Summers and Garry, 2010). Disruption of excitability of M1 following practise using inhibitory rTMS techniques did not influence the performance level or patterns of muscle activation in an aiming task (Shemmell *et al.*, 2007). Taken together, this evidence suggests that the outcome, but not the primary mechanism of learning resides in M1.

1.10 TMS-evoked measurement parameters associated with motor learning

The gold standard for interrogative excitability studies is by direct stimulation of the brain, which may be ethically possible when performed in waking humans during brain surgery (Kantelhardt *et al.*, 2010). Alternative, non-invasive observational techniques include positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imagery (MRI) and TMS (Kantelhardt *et al.*, 2010). However, TMS is the closest non-invasive proxy for direct cortical electrical stimulation (Chen *et al.*, 2008).

TMS is a non-invasive means of studying and manipulating alterations in cerebral function in vivo (Anand and Hotson, 2002; Daskalakis *et al.*, 2002). More specifically, it is a widely accepted means of evaluating short-lasting or plastic changes in the motor cortex consequent to practise or learning in healthy persons (Tinazzi *et al.*, 2003; Boroojerdi *et al.*, 2001b) or following neurological injury, including stroke and spinal injury (Hamzei *et al.*, 2006; Davey *et al.*, 1999). Electromagnetic pulses induce a secondary electric current of proportional magnitude in excitable tissues such as muscle and nerve (Rosler, 2001; Barker, 1999). Depolarisation of cortical neurons results in the generation of action potentials (Maeda and Pascual-Leone, 2003) which induces synchronous waves of stimulation in corticospinal

projections and motor units, to an extent dependent upon net excitability of this efferent network (Chen *et al.*, 2008). TMS magnetic pulses may be applied as single pulses or in pairs of pulses with variable intensity or inter-stimulus interval (ISI) as paired-pulse TMS to elicit different cortical effects (Kobayashi and Pascual-Leone, 2003; Maeda and Pascual-Leone, 2003).

Use of a standard, figure-of-8 coil stimulation coil placed on the scalp (Griskova *et al.*, 2006) is capable of stimulating an area of perhaps $3cm^2$ and penetrates between 2 to 3cm within the head, allowing focal cortical stimulation to take place (Barker, 1999) with a spatial resolution of between 5 and 10mm (Boroojerdi *et al.*, 2001b; Ashby *et al.*, 1999).The stimulation coils are placed over the M1 area of interest at 45° to the sagittal plane with the coil tangential to the scalp, an angle approximately perpendicular to the plane of the central sulcus (Kujirai *et al.*, 1993). The magnetic pulse induces an electrical current in the posterior-to-anterior direction, a direction perpendicular to the axons of descending pyramidal neurons but, crucially, and parallel to the plane of interneuron projections (Day *et al.*, 1989). Thus, in this orientation TMS preferentially stimulates both excitatory and inhibitory intracortical circuits (Day *et al.*, 1989), (Brocke *et al.*, 2005; Nakamura *et al.*, 1997).

Recent publications show that measures of cortical excitability evoked using magnetic fields generated by the hand-held, single round coil antenna are equally reliable and repeatable to those gathered using the twin coil (Badawy *et al.*, 2011). Furthermore, the coil is aligned to the measured vertex of the head for stimulation of all cortical representations, rather than to the site of greatest stimulation of each cortical representation as is required when using the twin coil antenna. The advantages of using a single coil antenna are therefore greater ease of handling and repeatability of measurements due to reduced sensitivity to inadvertent small changes in coil alignment relative to the scalp (Shimizu *et al.*, 1999).

MEP variability is essentially random across all frequencies and is dependent on temporally fluctuating and spontaneously changing excitability levels within the descending tracts (Kiers *et al.*, 1993). This variability appears to be inversely related to the factors of stimulus intensity, the level of background facilitation and the number of motoneurons recruited, while variability is reduced by increasing motoneuron excitability (Kiers *et al.*, 1993). Facilitation by voluntary activation also shortens the MEP latency and reduces the motor threshold (Rothwell *et al.*, 1987). Strong logarithmic associations appear to exist between force production and MEP facilitation (Davey *et al.*, 1999). The order of recruitment and rate coding of corticospinal volleys evoked by TMS is thought to be similar to that developed by voluntary activation (Bawa

and Lemon, 1993). As the corticospinal tracts are thought to be important for dextrous activity rather than force production (Colebatch and Gandevia, 1989) changes in these characteristic may be reflective of motor learning-related changes in the descending tracts.

Repetitive practise of motor tasks appears to be associated with topographical, plastic reorganisation of M1 and significant changes in kinematic coding of thumb movements as evoked by TMS (Butefisch, 2004; Caramia *et al.*, 2000; Classen *et al.*, 1998). Experimental studies have shown that retention ofhand representational area within M1 after cortical injury requires repetitive use of the impaired hand, while the size of the hand representation had decreased in primates who did not receive rehabilitative training (Friel, Heddings and Nudo, 2000). But increased use of the impaired limb appears to have a modulatory effect on plasticity in the surrounding tissue (Johansson, 2000). However, repetitive motor training alone does not produce functional reorganization of cortical maps. Instead, motor skill acquisition appears to be a prerequisite factor in driving representational plasticity in M1 (Nudo, Plautz and Milliken, 1997).

TMS-evoked stimulus-response curve (SRc) are considered to be a sensitive means of assessment excitability changes that take place in corticomotor pathways over successive measurement intervals (Boroojerdi *et al.*, 2001a), for example in measuring the changes in excitability of cortical representations of muscles involved in the acquisition of skilled training tasks (Pascual-Leone *et al.*, 1995a). In humans, improvement in the operation of motor skills correlates with progressive M1 reorganisation (Karni *et al.*, 1998). Indeed, functional magnetic resonance imaging (fMRI) studies show that mere passive joint mobilisation results in cortical reorganisation (Lotze *et al.*, 2003) an effect surpassed by active mobilisation (Perez *et al.*, 2004; Lotze *et al.*, 2003; Liepert *et al.*, 1998; Kaelin-Lang *et al.*, 2002) which implies that somatosensory afferent and voluntary drive are factors in motor learning, the latter being of particular importance.

With regard to long-term outcomes of skilled motor training, short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) evoked by probing with transcranial magnetic stimulation (TMS) measurement techniques are weakly expressed in the hand muscle of musicians compared to controls, both at rest and during activity (Nordstrom and Butler, 2002). This could represent a training-induced adaptation of corticospinal modulation related to enhanced dexterity (Rosenkranz *et al.*, 2005). SICI in particular is thought to reflect the net state of the balance between inhibition and excitation in intracortical circuits in M1, with maximum inhibition at around 2ms, and appears to reflect the state of synaptic activation

(Chen, Yung and Li, 2003). There is evidence that the phenomenon depends on gamma-Aminobutyric acid-ion channel receptor ($GABA_A$) mediated, synaptic inhibition in M1 (Kujirai *et al.*, 1993; Roshan, Paradiso and Chen, 2003; Ziemann *et al.*, 1996) which is thought to be important as a substrate of Brain-Derived Neurotrophic Factor (BDNF) dependent (Schjetnan and Escobar, 2012) long-term potentiation (LTP) -like plasticity (Hess, Aizenman and Donoghue, 1996). LTP is a mechanism thought to be instrumental in M1 cortical plasticity associated with motor learning (Ziemann *et al.*, 2001; Butefisch *et al.*, 2000).

Recent quasi-experimental work involving magnetic resonance spectroscopy (MRS) to assess changes in GABA concentration following anodal tDCS and motor activity found that GABA modulation in M1 was focal to the active cortical muscle representation immediately following both anodal tDCS application and motor learning (Stagg, Bachtiar and Johansen-Berg, 2011). Repetitive practise of motor tasks appears to be associated with topographical, plastic reorganisation of the M1 and significant changes in kinematic coding of thumb movements (Butefisch, 2004; Caramia *et al.*, 2000; Classen *et al.*, 1998). With regard to long-term outcomes of skilled motor training, SICI is weakly expressed in the hand muscle of musicians compared to controls, both at rest and during activity (Nordstrom and Butler, 2002). This could represent a training-induced adaptation of corticospinal modulation related to enhanced dexterity (Rosenkranz *et al.*, 2005). Thus, both motor practise and focal application of anodal tDCS at rest can give rise to increases in $GABA_A$ modulation (Stagg, Bachtiar and Johansen-Berg, 2011)

Short-term enhancement of performance in simple motor tasks has also been related to focal facilitation of MEP amplitudes (Muellbacher *et al.*, 2001) and reduction in SICI (Garry, Kamen and Nordstrom, 2004) evoked at M1 'hot spots' specific to the muscles involved in the motor activity, though high-intensity exercise might induce a reversible depression of cortical excitability (McKay *et al.*, 1995; Zanette *et al.*, 1995). Pharmacological studies using TMS as a measuring instrument indicate that drug-induced inhibition of glutaminergic synapses is shown to enhance SICI, a mechanism associated with deafferentation-induced plasticity in humans (Ziemann *et al.*, 2001). Practise of a skilled, isolated movement of the thumb enhances cortical excitability by significant reduction in SICI in hand muscle while increasing SICI in ordinarily synergistic muscles (Liepert *et al.*, 1998) indicating that specific changes in SICI as evoked by twin-pulse TMS techniques might underlie functional mediation of existing neural network excitability.

1.11 Definition for spatial motor skill and concept for measurement

Skill in any given task is both demonstrated and improved by practise (Yarrow, Brown and Krakauer, 2009). Both movement rate and spatial accuracy must be considered in measurements of skill (Reis *et al.*, 2009). Whereas performance is concerned with the quality of the execution of a physical activity, skill is defined by the capability to achieve a goal with speed and reliability of precision (Reis *et al.*, 2009; Parthornratt, Parkin and Jackson, 2011). We therefore define practical motor skill in the following terms**: *the ability to achieve a practical goal with spatial success over a limited quantity of time*.** Developing this statement, skill improvement is concerned with improving the accuracy rate, or productivity, in achieving the spatial goal target or a series of targets in a standardised routine of movements. It follows that, if participants are to be assessed on these criteria, the appropriate measurement system must detect and record both spatial and temporal domains with precision.

1.12 Definition for Task Productivity Rate (TPR) measurement

From the above definition of spatial motor skill, and extending the Fitts task concept of target standardisation to a task comprising of *n* targets of similar difficulty within a standardised sequential trial, we took task productivity to be the average time taken to achieve each successfully targeted score on an ideal standardised spatial target in a pre-defined sequential task. The measure of task productivity was termed as Task Productivity Rate (TPR). The beginning and end of each trial of the Motor Skill Rehabilitation Task (MSRT), developed as part of this project, is pre-defined and consists of a standardised series of grasping and prehension actions in relation to ideal, standardised targets (VII.2.9). The working definition for TPR was therefore taken to be ***'the measure of average time taken to achieve each successfully targeted score in a single trial of the Motor Skill Rehabilitation Task (MSRT)'***. This interval scale measure was calculated as the count of successful targeting events observed divided by the overall trial completion time, with unit of measure seconds per score and was summarised as an arithmetic mean value over the number of trials stated in the Methods section of each respective study.

1.13 Rationale for focusing on changes to non-dominant upper limb function

Previous studies suggest that the effects of motor learning and the adjunctive intervention might be detected more readily in relation to the non-dominant limb. But the mechanisms underlying functional dominance appear to be complex and the role of lateralisation is uncertain in relation to motor learning. In fact, the effects of anodal tDCS upon motor skill learning may be particularly evident when applied to the non-dominant cortex, hence allowing for assessment of effect with limited subject exposure. Boggio et al (2006), found more pronounced and significantly more beneficial effects upon motor learning outcomes compared to sham in the non-dominant hand but not the dominant hand, possibly due to non-use of the non-dominant hand in dextrous tasks (Boggio *et al.*, 2006a). In healthy persons also, the control of precise hand movements using the non-dominant hand was enhanced both immediately after and 30 minutes after application of anodal tDCS to the contralateral primary M1 (Matsuo *et al.*, 2011).

Though the left hemisphere is thought to be dominant in the control of complex skills (Serrien and Spape, 2009) it has been argued that reduced functional connectivity in the non-dominant hemisphere may underlie interhemispheric differences in fine motor control although the direction of causality was not established (Reilly and Hammond, 2006). Twin-pulse TMS studies determined that non-dominant hemisphere intracortical excitability was reduced compared to the contralateral side and appeared to be due to differences in intrinsic connectivity (De Gennaro *et al.*, 2004). Laterality-dependent differences in hand path kinematics are reflected by asymmetries in EMG activity and resultant torque patterns suggesting that the dominant limb has a relatively refined muscle activation strategy, which may mean that different neural control mechanisms govern movement of dominant and non-dominant upper limbs(Bagesteiro and Sainburg, 2002).

These findings could be contingent upon the history of prior skills learning and may not reflect the capacity for future learning. Studies investigating the comparative effect of anodal tDCS upon dominant and non-dominant hemispheres have found greater excitability changes in the cortical representation of the non-dominant upper limb target muscle due to the intervention (Vines, Cerruti and Schlaug, 2008). Similarly, assessment of single-pulse MEP facilitation in a hand muscle at rest did not reveal handedness-related differences in amplitude, but activity-related facilitation of MEPs was larger in the left non-dominant muscle relative to the dominant muscle. However, this difference may have been related to muscle strength rather

than skill as demonstrated in a finger-tapping task and pegboard testing which might simply reflect differences in activity secondary to hand preference (Brouwer, Sale and Nordstrom, 2001). Alternatively, in single-pulse TMS evaluation of a facilitated hand muscle there was a significantly increased cortical silent period from the non-dominant representation relative to the dominant side. Because the cortical silent period is thought to be associated with preferential stimulation of inhibitory intracortical circuits, it could be that the inhibitory circuits of the non-dominant hemisphere are relatively more excitable (Priori *et al.*, 1999) providing a possible mechanism whereby greater functional improvements can be shown in the non-dominant limb.

There may therefore be additional potential for non-invasive brain stimulation in overcoming the possible secondary effects of under-use in dextrous tasks (Boggio *et al.*, 2006a) consistent with significantly reduced rates of environmental adaption (Schabowsky, Hidler and Lum, 2007) and fluency of limb dynamics (Sainburg and Kalakanis, 2000) found in the non-dominant relative to dominant upper limb, but which appear unrelated to power development (Reilly and Hammond, 2006). For these reasons we focused on function of the non-dominant upper limb, which remains an important target for rehabilitation.

1.14 Justification for studying the effect of anodal tDCS upon recovery of upper limb function in incomplete tetraplegic spinal cord injury

The rehabilitation of upper limb motor control in the incomplete cervical spinal injured individual presents the similar challenges as it would in healthy subjects. Both groups share intact brain structures with the capacity for memory, experiential learning and planning. However, the incomplete lesioning of sensory and/or motor tracts at the spinal level leaves individually variable and unique levels of functioning at and below the level of the lesion, with concomitant structural changes in corticomotor regions (Wrigley *et al.*, 2009).

Findings in patient groups and healthy individuals indicate that anodal tDCS is a non-invasive brain stimulation intervention which is safe and has produced promising experimental results by enhancing the extent and/or rate of use-dependent primary motor cortical neuroplasticity achieved by task practise (Williams, Imamura and Fregni, 2009; Reis *et al.*, 2009). The effect upon behavioural outcomes is also positive in improving skill acquisition and retention (Reis *et al.*, 2009). This direct relationship between anodal tDCS dosage and the acceleration and retention of practise-dependent skill improvement has been emphasised by experimental demonstrations of positive action on areas of the brain shown by fMRI imaging to be associated with cognitive processes (Clark *et al.*, 2012). The findings with respect to changes in peripheral excitability may also impact beneficially upon impairments giving rise to spasticity (Roche *et al.*, 2009). However, it is as yet a matter for enquiry whether tDCS is a beneficial adjunct treatment during rehabilitation therapy in SCI populations (Thickbroom and Mastaglia, 2009).

Resolution of post-injury diaschisis (Finger, Koehler and Jagella, 2004), rather than peri-insult reorganisation, is thought to be one of the important mechanisms by which functional recovery occurs in stroke patients (Webster, Celnik and Cohen, 2006), a phenomenon similar to that observed over the time-course post-SCI due to spontaneous recovery (Jurkiewicz *et al.*, 2007) or targeted intervention (Hoffman and Field-Fote, 2007). These results suggest that the efficacy of tDCS lies in augmentation of residual healthy neurological function to drive plasticity, rather than a primary regenerative effect upon the lesion itself. Repetitive task-oriented training has been shown to evoke cortical reorganisation in both stroke (Gauthier *et al.*, 2008; Liepert *et al.*, 2000) and incomplete SCI patients (Beekhuizen and Field-Fote, 2008; Hoffman and Field-Fote, 2007), in the latter group alongside adjunctive modalities. Daily dosage of anodal tDCS adjunctive to rehabilitative tasks appears to have a cumulative effect in

evoking statistically-significant, lasting improvements in functional outcomes in healthy (Reis *et al.*, 2009) Parkinsons Disease (Fregni *et al.*, 2006b) and stroke (Boggio *et al.*, 2007) subjects compared to sham stimulation protocols. Changes in a specifically-developed repetitive motor task and skill outcome measure provided for assessment of changes in dexterity as the function of speed and accuracy and revealed significantly enhanced between-sessions consolidation of motor memory in learning the novel skill, resulting in a persistently enhanced task score up to 3 month follow-up (Reis *et al.*, 2009).

There is an established body of evidence supporting use of tDCS modalities to improve manual function following stroke (Constantinescu *et al.*, 2010) but the application of non-invasive brain stimulation modalities is very limited in spinal injured populations. A small-scale pilot using a group sequential study design including incomplete stable SCI patients has suggested the beneficial effect of rTMS protocols in improving upper limb functional outcomes, corticospinal strength and measures of sensory status evoked at hand muscles (Belci *et al.*, 2004). Though the methodology of the study confounds the separate analysis of the rTMS factor and the use of repeated functional outcome measurements throughout the period of the study, the findings of that study may reflect an accelerated rate of task-dependent sensorimotor plasticity which may be attributable to the adjunctive implementation of rTMS. Thus, there is limited evidence that non-invasive facilitatory stimulation of the cortex may have a beneficial effect on the functional status and associated corticomotor connectivity in this patient group.

1.15 Rationale for applying constraint-free practise during training in healthy or neurologically impaired populations

In the current project a constrained-workspace training paradigm was applied, whereby participants were instructed to achieve the behavioural outcomes of the MSRT task but were free to assume any pattern of movement in prehension towards achieving the sequential, spatial behavioural goal. That is, we did not attempt to enforce any form of idealised movement pattern, such as might be applied in a robot-assisted motor rehabilitation scenario (Marchal-Crespo and Reinkensmeyer, 2009). It was considered important to allow participants, whether healthy or SCI tetraplegic, to evolve motor skill in as naturalistic fashion as possible in order to avoid introducing a possible confounding factor in motor learning. For example, in chronic tetraplegic SCI subjects, though movement patterns in solution of a motor task are diverse and governed by the requirements of the activity they are nonetheless limited by the

nature of the individual injury (Jacquier-Bret, Rezzoug and Gorce, 2008; Hoffmann *et al.*, 2006). The enforcement of movement patterns that are not directly concerned with acquisition of the spatial target could inhibit the construction of an accurate inverse internal map which is necessary for skill formation in unconstrained practise in SCI as well as healthy persons (Casadio *et al.*, 2010). To date, a single pilot study has shown that, even when the robot control parameters were individually tuned to the capabilities of sub-acute cervical SCI participants the outcome of training of the trained arm was not significantly different to the functionality change in the untrained, contralateral arm control (Zariffa *et al.*, 2012). Given that the effects of the injury upon sensorimotor function may differ widely in incomplete SCI (de los Reyes-Guzman *et al.*, 2010) but skill learning capacity is thought to be an independent factor when muscle force production capacity is accounted for (van Hedel, Wirth and Curt, 2010) then it was considered that introduction of any type of patterning constraint could at best have no effect upon the dependent outcome, or worse inadvertently become a confounding interventional variable, affording a unnecessary source of bias to the results of the following studies.

1.16 Summary

Reinstatement of upper limb functional independence lies amongst the highest priorities in the growing population of tetraplegic spinal cord injured persons. Acute injury to the spinal cord is followed by processes which begin within hours of the injury and may continue over the period of years, including disruption in activity of the wider neural network. Patterns of cortical neural representations projecting to functionally preserved muscles above the level of the injury are expanded at the expense of those below the representation. These abnormal patterns of brain activation persist in both complete and incompletely injured SCI subjects. The diverse presentation of motor and sensory issues affecting the upper limbs of incomplete tetraplegic persons has a detrimental effect on the ability to make short-term feedback-derived adaptions and fractionation of movements which are important for fine motor dexterity. These persons may be particularly reliant on the formation of feed-forward models to improve performance in achieving goal-directed tasks, and therefore may derive particular benefit from adjunctive application of anodal tDCS.

Addressing maladaptive neuroplastic changes may conversely provide a physiological basis for task-dependent functional recovery in chronic SCI patients. Therapeutic interventions can improve manual dexterity in healthy and neurologically-impaired states when intensive, structured task-specific training is employed. Many areas of the brain are important in the process of motor learning but *in vitro* and *in vivo* studies in animal models and imaging and excitability studies in humans suggest that activations of the contralateral primary M1 during voluntary activity are strongly associated with the uptake and retention of new motor patterns. Anodal transcranial current stimulation (tDCS), when applied to the primary M1 is a brain stimulation modality which is thought to act primarily upon processes underlying motor learning. This safe and painless technique has been shown to be successful in producing short-term improvements in the practical motor tasks in healthy and stroke-affected humans, and there is some evidence to suggest long-lasting retention of a skill attributable to adjunctively-applied anodal tDCS. However, there are central issues with the nature and interpretations of the outcome measures applied. Furthermore, the neurophysiological changes which might underpin long-term changes in behaviour following application of this adjunctive intervention, which is active only for short periods of time, are unknown.

The central questions within this project relate to whether anodal tDCS might have a beneficial effect upon outcomes associated with motor learning in rehabilitation from incomplete spinal cord injury, and whether the findings are generalizable to the population at large. But there is

evidently a substantial amount of work to be done in order to ensure that the measurement systems employed are both valid and practical for implementation to measure the parameters of interest. In order to quantify changes in spatial goal-oriented motor skillit is necessary to apply a training paradigm which provides both for the development and outcome measurement of a practical spatial motor skill in response to training.

1.17 Research questions

We asked whether parameters of learning in complex manual dexterity tasks are modified by anodal tDCS in incomplete tetraplegic SCI persons, whether the effects are generalizable in the wider population and what the underlying neurophysiological correlates of these changes might be.

1.17.1 Research question 1

Does adjunctively applied anodal tDCS alter the uptake and lasting retention of practical motor skilled behaviour in incompletely-injured tetraplegic spinal cord injured adult humans?

1.17.2 Research question 2

Are the behavioural findings generalizable out to healthy human adults?

1.17.3 Research question 3

Does the intervention have a demonstrable lasting effect upon the excitability of M1 associated with motor skill acquisition in healthy persons?

Chapter 2. General Methods

2.1 Introduction

In order to address the research questions emergent from the literature review a series of studies was carried out, each of which build upon the findings of the former towards the general conclusions. The general methods detailed below are applied where reported in the relevant chapters, with specific variations in techniques and protocols expanded upon.

2.2 General ethical requirements and recruitment of healthy persons

All activities were designed and carried out in accordance with the Declaration of Helsinki. Guidelines, practises and procedures were adopted from Brunel University Research Ethics Committee Research Ethics Handbook (Brunel University London, 2012). Formal ethical approval for all studies presented in the current project was sought was granted by the Research Ethics Committee of the School of Health Sciences and Social Care, Brunel University London.

For research including NHS patients on the NHS research site, the London Spinal Cord Injury Centre, Royal National Orthopaedic Hospital NHS Trust, Stanmore, Middlesex HA7 4LP (Study 2) the researcher undertook an NHS Good Clinical Practise in Research course and completed the process of obtaining an NHS Research Passport. Additional ethical approvals were applied for via the UK National Integrated Research Application System (NHS, 2012)and granted from NHS Local Research Ethics Committees and the Site Research and Development manager as required.

For Study 1 and 3all participant contact took place in the laboratory facility in Mary Seacole Building, Uxbridge campus, Brunel University London, UB8 3PH, UK. Participants were recruited from the staff and student populations at Brunel University by e-mail and poster advertisement. Participants who expressed an interest in the research received an ethically-approved participant information sheet prior to attending the first study session. Details of the study were provided in the information sheet along with the statement that participation was completely voluntary with the right to free withdrawal at any time.

All participants were provided with an information sheet prior to inclusion in the study and gave informed consent to take part. As a standard element of each study protocol, participants were provided with a signed copy of the primary consent form signed by the researcher. In Study 2, a patient information sheet and duplicate signed copy of the consent form was inserted into the participant's medical notes at the hospital site. In repeated-measures study designs, participants filled in health screening questionnaires and signed to re-establish consent at the commencement of each study session.

For participation in Studies 1 and 2, volunteers received no payment or favour in return for taking part. For Study 2, travel expenses were paid for travel between the study site and the home address at a level dictated by Brunel University transport reimbursement policy. For Study 3, participants received £35 Sterling in cash on condition of full completion of the 9-day study protocol. These expenses were met by the researcher in the first instance and repaid under the conditions of the Brunel University Isambard Postgraduate Research Scholarship, of which the research was a recipient for the course of the current project.

2.3 Additional recruitment criteria and assessment of spinal cord injured subjects for inclusion in pilot study

2.3.1 Participant recruitment

For Study 2, London Spinal Cord Injury Centre medical records were accessed by permission and screened. An invitation letter and participant information sheet was sent to individuals meeting primary inclusion criteria and where exclusion criteria did not apply. Individuals who responded and expressed an interest in taking part were invited to an assessment session where fitness to take part was established, including cognitive fitness baseline manual capacity, handedness and characterisation of physical capacities. Proformas may be found at Appendix E.

Inclusion criteria were: cervical level C5-C7 inclusive at classification C or D; post-injury duration more than 12 months; age 18-70 years; right-hand dominance pre-injury; ability to pick up a small object from a table surface using the left hand only; stable medical condition. Exclusion criteria were: history of severe head injury or surgery to the head, or of surgery to the left arm; severe, uncorrected visual impairment; pregnancy. Following collation from a number of separate databases summarising close to 1500 separate treatment episodes, 41

candidates were identified from patient notes and invited to take part in the study. 27 electively declined to take part, including 11 non-responders, as summarised in Table 2.1.

6 individuals were excluded due to medical, physical or social factors detected subsequent to initial contact. The final included sample size was 8. The descriptives of the 8 volunteers (of which 3 females; mean age 50.6; mean time post-injury 111.6 mo) are shown in Table 4.1.

Table 2.1: Reason categories for non-participation in the current study.

Volunteers were excluded because they failed to meet the inclusion criteria for the study, or declined to take part.

PARTICIPATED	8	
DID NOT PARTICIPATE	33	
Reason:	Excluded	Declined
Too busy		4
Neuro level	1	
Previous participation		2
Too far to study site		3
Left handed	1	
Unstable medical issues	1	
Insufficient reward		1
Psychiatric treatment	1	
Safety concerns		1
No response		11
No reason		4
Not interested		1
Inadequate English	2	
Subtotals	*6*	*27*

2.3.2 Assessment

All participants agreed to a physical and cognitive assessment prior to commencement of the study protocol. This included assessment of sensory and motor preservation of the non-dominant upper limb and shoulder girdle, including sensitivity to sharp and blunt pressure, assessed according to the International Standards for Neurological Classification of Spinal Cord Injured Patients (ASIA, 2011) (VII.2.3.3) As a requisite for inclusion in the study each individual completed part 1 of the General Practitioner Assessment of Cognition (Brodaty, Pond et al. 2002), a quick and simple, relatively bias-free questionnaire to evaluate threshold cognitive disability (Brodaty, Kemp and Low, 2004),Appendix E. Handedness was assessed using the

Edinburgh Handedness Inventory (modified) for table-top activities appropriate to the population and the study theme (VII.2.4). One patient, assigned to the SHAM group, reported himself as right-hand dominant pre-injury and left-hand dominant post-injury (Table 4.1). However, it subsequently emerged that this patient undertook the majority of prehensile tasks bimanually and was otherwise highly reliant on a carer for self-care activities including feeding.

2.3.3 Assessment of sensory and motor impairment

Evaluation of sensory and motor sparing was carried out during Study 2 according to the International Standards for Neurological Classification of Spinal Cord Injured Patients, otherwise termed as the American Spinal Injury Association (ASIA) standards. This evaluating system captures the level and severity of neurological injury on ordinal scales using the ASIA Impairment Scale (AIS) (ASIA, 2011). This has been shown to be an appropriate instrument for discriminating between SCI patients (Furlan *et al.*, 2008).

The examination was carried out on the non-dominant upper limb only, using the format laid out in the ASIA AIS assessment form (Appendix E).

For sensory testing, discrimination of sharp and blunt pressure was made using NeuroTips sensory threshold test disposables (Art. OWNT5405, Morton Medical.Co., GL7 6PY, United Kingdom). Sensitivity to light pressure was made using cotton wool pads.

2.3.4 Assessment of cognition

The General Practitioner's Assessment of Cognition (GPCOG) validated cognitive test (Brodaty, Kemp and Low, 2004; Brodaty *et al.*, 2002)was included as a screening tool in Study 2 to confirm that participants were able to understand, memorise and recall information at a level considered healthy in the general population. This standardised test was applied during the Assessment session, with a perfect score set as an inclusion criterion (proforma, Appendix E).

2.4 Assessment of handedness

A modified version of The Edinburgh Handedness Inventory (Oldfield, 1971) assessment tool was applied to objectively confirm that the factor of hand dominance was unlikely to be a confounding factor in project studies. The full screening tool was considered to be of limited applicability in the event of tetraplegic functional impairment, as the conventional format evaluates handedness over a range of activities which include whole-body movements. The standard assessment format was amended to reduce the number of activity categories to

reflect upper limb function in bench side activities, and was applied as a standardised handedness assessment for studies 1, 2 and 4. The format used is presented as the Edinburgh Handedness Inventory (modified) (Appendix E). In total, the categories scored for handedness were: writing; throwing; scissors; toothbrush; knife (without fork); spoon; match (when striking); use of a computer mouse.

Hand preference has been shown to be distributed discretely rather than continuously, in large population samples (Dragovic, Milenkovic and Hammond, 2008). Dragovic (Dragovic, 2004) critiques the psychometric properties of the Edinburgh Handedness Inventory and advances an argument, based on the outcome of regression and correlational analyses on a large-sample dataset, for reducing the number of items to 7. This process incidentally dispenses with all those items routinely carried out in the standing position, which might be considered an irrelevant and disturbing concept for non-ambulatory tetraplegics. The systematic exclusion of ambiguous, redundant or irrelevant items to focus on discrete unimanual activities improved the validity and internal consistency of the Inventory in predicting laterality and degree of handedness (Dragovic, 2004). As recommended as a modern and ubiquitous hand functions (Dragovic, 2004) computer mouse usage, an activity important in supporting the lifestyle of both healthy and tetraplegic SCI individuals (Goodman *et al.*, 2008; Hall *et al.*, 1999) was included as an additional category.

2.5 Evaluation of blinding to the intervention and subjective measures of perception

In order to evaluate whether blinding measure were successful during interventional studies, and to provide for evaluation of mild adverse effects, participants were asked to complete subjective questionnaires at the end of each intervention session and at the commencement of the subsequent session. Perception categories were presented after the method of Poreisz and colleagues (Poreisz *et al.*, 2007), on 5-point numerical rating scales (NRS) with an additional 'no perception' response category. Judgment of blinding in response to direct questioning was made on a 5-point NRS (Appendix E) with analysis by non-parametric, asymptotic Mann-Whitney U tests applied under each perception category.

The findings of these analyses were that overt concealment of participants to the intervention was preserved both in Studies 2 and 3. No incidences of adverse sensory effects were reported.

2.6 Study designs

All studies presented were prospective and quantitative in nature. Each study involved the application of TMS-based neurophysiological measures, behavioural measures or both, and with additional subjective measures of perception where relevant. Two studies involved validation of outcome measures and applied a within-subjects design in a single cohort of volunteers, to overcome issues of variability between individuals and increase the potential to detect the effect of changes in independent variables (Field, 2005).

A further two studies were of randomised control trial, experimental design. The quantitative, between-group sham/placebo-controlled experimental study design is the preferred methodological model for investigating the lasting effects of interventions upon human participants (Sibbald and Roland, 1998). In these a between-subjects format was necessary as the combined effect of training protocol and group allocation which if, for example a cross-over design was applied was considered likely to induce a complex long-lasting order effect of motor learning which could mask the effect of the intervention (Hicks, 2005). The applications of repeated-measures protocols differed across studies in accordance with the objectives, and are detailed in each chapter.

2.7 Online and offline effects in motor learning

Motor learning is known to take place both during skill acquisition, or motor practise and is termed as an 'on-line' effect (Korman *et al.*, 2003). Consolidation of the motor skill takes place in the hours and days following practise and is considered to be an 'offline' effect (Robertson, Press and Pascual-Leone, 2005). Thus, measurement at the beginning of a subsequent measurement session represents overall skill retention as the combined result of previous 'online' acquisition and 'offline' consolidation effects. By this definition, all measurements of TPR were on-line, as measurement of the skill parameters took place during MSRT practise which also constituted the training paradigm. However, others have utilised a similar paradigm of task-dependent learning and skill measurement and considered task practise at the start of practise sessions to represent retained skill as a combined 'on-line' and 'offline' effect (Reis *et al.*, 2009) and this is the definition applied in the current project.

2.8 Approach to establishment of task-dependent skill baseline measures

The aim of the project was to assess the adjunctive effect of anodal tDCS on learning behaviour from the naïve state to control for the possible effect of prior skill learning. In order to achieve this, we adopted a similar approach to Stagg and colleagues, where the DC stimulation mode, performances of the task from the naïve state and baseline measurement was commenced concurrently (Stagg *et al.*, 2011). The primary effect of anodal tDCS arises as a result of static electrical field polarisation which arise following a period of several minutes' stimulation, which when applied via surface electrodes to M1 in the current montage enhances the spontaneous firing rate of corticospinal neurons (Nitsche *et al.*, 2008). It is unclear at which point functional effects become apparent, as those RCT or cross-over studies employing functional outcome measures apply measurement intervals before and after stimulation which is typically not less than 20 minutes in duration (Hummel *et al.*, 2010; Kim *et al.*, 2009; Boggio *et al.*, 2007). 5 minutes of 1mA anodal tDCS stimulation increases cortical excitability for only 5 minutes beyond the stimulation period (Nitsche and Paulus, 2000; Fricke *et al.*, 2011) with 7 minutes and 10 minutes of stimulation producing 20 and 30 minutes corticomotor enhancement of MEPs, respectively (Fricke *et al.*, 2011). In summary, because the effects on cortical excitability and behaviour are not immediate and the noisy, stochastic nature of skill led us to take samples over large numbers of consecutive trials which also has the effect of controlling for short term variations in the TPR outcome, the risks of bias were weighed against the aims of the project and it was decided that there was not a substantial risk of biasing the results, and if there were it would be in favour of the null hypothesis.

2.9 Motor Skill Rehabilitation skill Task (MSRT)

2.9.1 Development of a univariate measure of task-dependent motor skill

2.9.1.1 Implications of Fitts' Law for feedback of target error in a sequential task

From the concept of *n* identical targets with the same fixed I_D within the trial, this introduced a potential for non-linearity in the measurement as follows. Recall that, from Equation 1.8-3, if a participant's movement time drops below the critical threshold *t* the I_P for the target will be exceeded and, on average, aiming reliability falls. As failure rates on all *n* identical targets increase the effect on a sequential task measure will be multiplicative, hence non-linear.

Systematic planning corrections require reliable on-going feedback of prior error. If motor adaption (van Beers, 2009) and learning (Novick and Vaadia, 2011)is thought to be mediated partially by error-based feedback modalities (Diedrichsen *et al.*, 2010). If feedback of error performance is strongly non-linear, as is theorised in the single I_D binary outcome target scenario, or not clearly defined, as in continuous distance from a target centre for example (MacKenzie and Isokoski, 2008)then cognition of performance to sub-serve the behavioural goal might be difficult for individuals to achieve. Naturalistic feedback modes would ideally be preserved if we hoped to generalize observations in respect of motor skill learning.

As a strategy for improving the linearity of a measurement scale targets in a sequential measurement task where we also wished to encourage natural processes of motor learning, it was then desirable to subtly exploit I_D and thus the I_P -mediated performance 'failure threshold' across a target array, to create a *weighted scale* of error probability within which a participant can operate. In order to maintain outcome probabilities, however, the net index of difficulty for the entire task needed to remain unchanged under random assignment of motor sequences to control for order and positioning effects, which are known to affect movement times to some extent (Pratt, Adam and Fischer, 2007). Thus, the information required to attain the totality of targets (I_P, or TPR as we term it) should remain the same.

2.9.1.2 Implementation in a practical sequential task

As an approach to the modulation of target difficulty I_D, It was then considered desirable that the physical construction of the array of *n* targets should remain identical as regards target dimension no matter what the order of the motor sequence, as altering target size in a

ubiquitous task might be difficult to implement. As an alternative to modifying the form of the targets, we considered that it might be possible to modulate I_D on individual targets by manipulating the biomechanical properties of targets i.e. manipulating the physical dimensions as they present to the participant to create subtle variations in prehension difficulty. With this rationale, the I_D of the target would be increased for relatively more 'difficult' target grasp strategies. A further potential advantage of this orientation approach to varying target difficulty was that grasp orientation in the transverse plane could be achieved using multiple combinations of joints at the level of the hand, forearm and shoulder thus providing for motor redundancy to offer a participant flexible solutions to the movement problem (Wong and Whishaw, 2004; Hoffmann *et al.*, 2006).

2.9.1.3 Generic task criteria

The generic criteria for functional tests outlined by Van Tuijl (van Tuijl, Janssen-Potten and Seelen, 2002) include the following:

1. All tests items can be performed by the target participant group;
2. The items are not too long or too arduous.
3. The test can be administered in a short period of time
4. The test is sensitive across different participant groups and within participants over time;
5. The test resembles a functional task.
6. The test elicits compound movements of the upper limb arm and hand joints.
7. Involves repetitive movements.
8. Provides clear start and end points.

2.9.1.4 Key criteria for a sequential target-matching skill training and measurement task

1. Simplicity of use – minimum declarative learning required.
2. The test is sensitive to learning.
3. Ease of use
    - Participants – it is a prerequisite for skill measures that some level of grasp function is preserved, but as the aim is to test motor learning not grasp ability

the object for prehension must be light and of appropriate dimensions for manipulation by both healthy persons and grasp-impaired persons.

- Investigator – outcomes are easily and objectively recorded and minimum time is taken to reset the task for unbroken blocks of repetitions.

4. Define and constrain activity within workspace areas.
5. Minimise potential for confounding sequential and order effects.
6. Present a sequence of individual trials.
7. Provide a difficulty scale to facilitate a broad range and sensitivity of measure, while providing subjects with clear error feedback where it occurs.
8. Provide a sequence of several identical task elements, which are variable in a single domain to manipulate the target difficulty I_D without altering component geometries.
9. Geometries should unequivocally define spatial error limits and provide clear feedback.
10. Facilitate delivery of TPR skill outcome measure

    - Provide objective measures of spatial error and completion time, with clear feedback to participants and investigators.
    - Systems must allow motor skill score to be recorded by trial and over time.

2.9.2 User involvement in evaluation and development of prototype MSRT apparatus

During the months between August and October 2009 a total of 4 right-handed adult volunteer acquaintances of the researcher gave of their time freely and informally to aid in the evaluation and development of the MSRT sequential target matching task. 2 of these volunteers had demonstrable hand function impairments and were able to report having been classified with sensorimotor deficits by medical professionals below the neurological spinal cord injury level indicated.

Baseline measurements were gathered following minimal prior practise from the naïve state. Volunteers were asked to work as accurately and rapidly as possible, using the non-dominant upper limb and any grasp of choice. 3 volunteers took part in protocol A: 10 task trials in rapid succession, on 2 consecutive days, on a prototype task (Figure 2.1). A single volunteer completed protocol B: On 3 consecutive days, 3 blocks of 10 task trials in rapid succession, each block separated by rests of approximately 1 minute, on the definitive task apparatus (Figure 2.2).

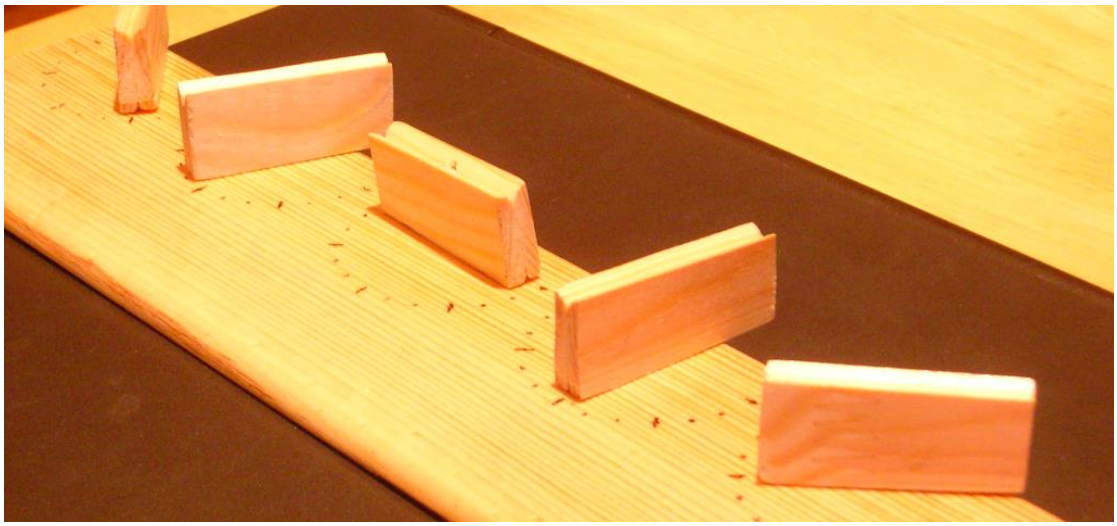


Figure 2.1: Prototype apparatus for the MSRT.

Gross geometric parameters were finalised during evaluation trials with healthy persons and tetraplegic persons. Volunteers completed trials by successively grapsing 8x35mm cylindrical wooden pegs and placing in order from left to right, as quickly and accurately as possible. Trial duration was measured using a handheld stopwatch. Subsequently, a central slot was introduced across rail centres to dichotomise success/failure outcomes and implement the concept of varying target difficulty through biomechanical constraint. The layout was also subsequently clustered in order to control for effects of layout on movement times.

Table 2.2: Descriptives of volunteers and results of participation in MSRT prototype evaluation.

Protocol A: prototype apparatus, 10 task trials in rapid succession, on 2 consecutive days. Protocol B: definive MSRT apparatus practised on 3 consecutive days, 3 blocks of 10 task trials in rapid succession, each block separated by rests of approximately 1 minute. American Spinal Cord Injury Assessment Impairment Scale (ASIA AIS) as reported by volunteer. Final day score: normalised to provide comparison of learning effect. Group mean final day score was calculated from normalised Protocol A final day scores, indicating the group mean learning effect.

	Descriptives			***Results***			***Final day score normalised to baseline (ratio)***
protocol	*Impairment (level)*	*Gender M/F*	*Age (yrs)*	*TPR score (s/score)*			
				Day 1	*Day 2*	*Day 3*	
A	Tetraplegic (C5 D)	F	27	34.40	31.50	n/a	0.92
	Tetraplegic (C7 D)	M	47	18.49	21.43	n/a	1.16
	Healthy	M	25	1.81	1.53	n/a	0.84
	Protocol A group mean normalised final day score						**0.97**
B	Healthy	F	33	1.936	1.542	1.505	0.78

All participants managed to achieve at least one correct target placement per trial. From Table 2.2 we see that participants with upper limb deficits have longer trial durations than healthy persons. Despite this, each volunteer taking part in protocol A maintained performance over 2 consecutive days although individual variabilities suggests that the taking of TPR performance averages should include more trials to provide a more reliable measure of skilled attainment. The group average normalised score compared to baseline, at 0.97, further suggesting that, at a 3% improvement on average, 10 task practise trials were not sufficient to induce a use-dependent learning effect.

The single volunteer taking part in protocol B was assigned a more intensive dosage of task practise. This proved sufficient to induce substantial learning (28% improvement in TPR score) over 3 consecutive days with the greatest improvement in skill between day 1 and 2.

2.9.3 Design features and target parameters of the definitive MSRT task

Form and colour was used to respectively physically and cognitively demarcate the general areas of the MSRT– start-stop button, peg dish and target areas. The use of a modular design allowed for rapid replacement of pegs in the receiver dish by the investigator, preventing potential interference with peg position by participants and modification of target rail alignment to new sequence order positions (Figure 2.2).

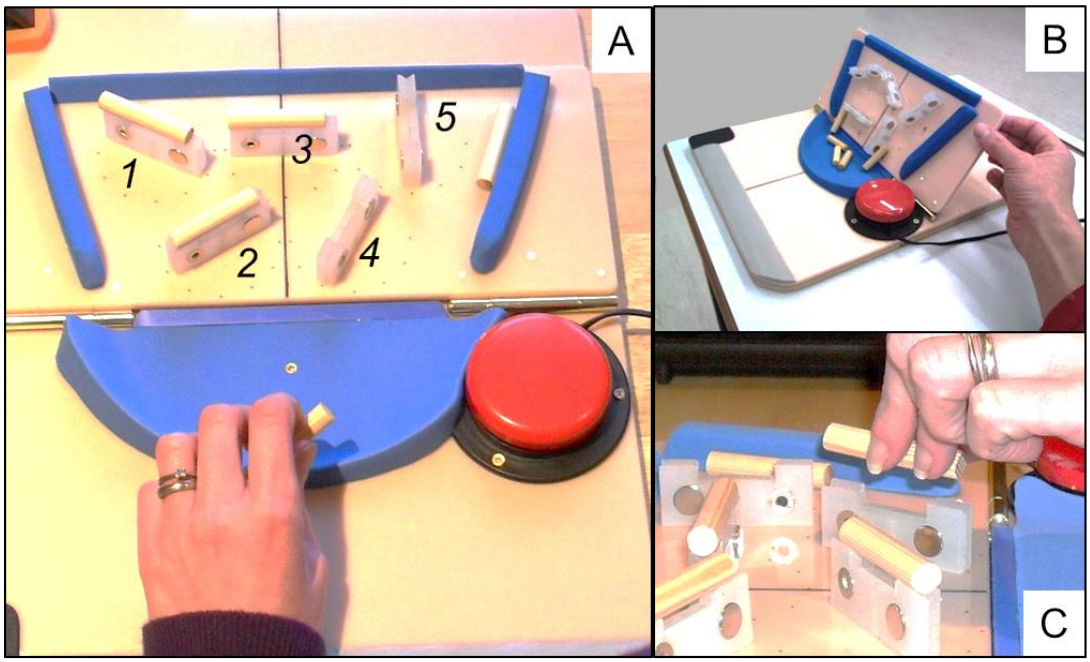


Figure 2.2: Motor Skill Rehabilitation Task (MSRT).

All activities are carried out with respect to the left upper limb. A) Pegs are grasped from the dish and placed on rails in consecutive order from left to right (1 through 5). Illustrated are respective rail orientation angles 120°, 60°, 90°, 30° and 0° with respect to the centre line of the apparatus (black line). The participant triggers the start and end of each trial via the red start/stop button. B) The investigator tilts the rail mounting board to return the pegs to the receiver dish. c): Geometric properties of target rail elements can be manipulated to vary the index of difficult of the sub-task element by changing angular orientation, after loosening the wing-nut retainer.

Experience of the prototype evaluation also informed the design of the definitive apparatus. For example, it became apparent that in this state the outcome was not reliably sensitive to orientation because the effective target length was not constrained in the longitudinal axis. Altering the rail design to incorporate a central groove solved this issue, which had the effect both of enforcing a direct relationship between relative peg/target orientation and effective target dimensions (Figure 2.7) and area (Figure 2.8) and dichotomising outcomes clearly into visual evidence of success or failure (Figure 2.3).This also provided for stringent management of reverse kinematic control of grasp orientation limits across the range of target presentation orientations (Figure 2.4).

The interaction of rail and peg geometries makes target difficulty strongly contingent on the angular match between the longitudinal axes of the receiver rail and approaching peg (Figure 2.5) where a systematic linear relationship exists between angular deviation and target area (Figure 2.6, Figure 2.7, Figure 2.8). In healthy persons, accurate aiming towards target position is thought to be a function of the proximal muscles while angular refinement takes place independently at the wrist and fingers (Soechting, 1984) but the expression of effective movement strategies in those with existing functional deficits may be less clearly defined. Note that the dimensions of the effective target (width, length, target area) are covert, that is, exist only in the free space *between* the raised support areas (Figure 2.5). This feature increases the spatial difficulty of the task as the target centre position can only be inferred from the relative positioning of the rail supports and the ends of the grasped peg during reaching. Participants remain naïve to these principles and are instructed simply to try and place a peg across both the raised rails in sequential order, as quickly/accurately as possible. Thus, each individual is left to develop a strategy for positional and rotational congruence in a purely procedural fashion.

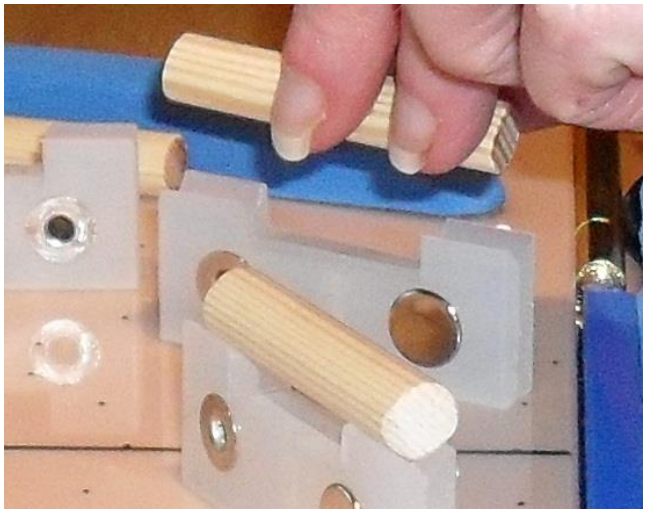


Figure 2.3: Detail of rail and peg placement.

Rails are engineered with a central groove to securely capture correctly-placed pegs and a central recession across the rail to limit the longitudinal length dimension of the target footprint. Error is scored if a peg fails to retain contact with both raised rail areas following release. Pegs are 8mm diameter x 35mm in length.

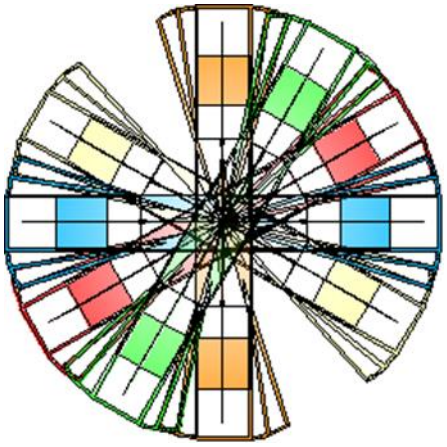


Figure 2.4: Schematic indicating overlay of MSRT rail target orientations.

30^{o} rail orientation intervals: 0,30,60,90,120°, with 5.2^{o} error margin overlay between consecutive orientation angles. 0° orientation lies vertically on the page.

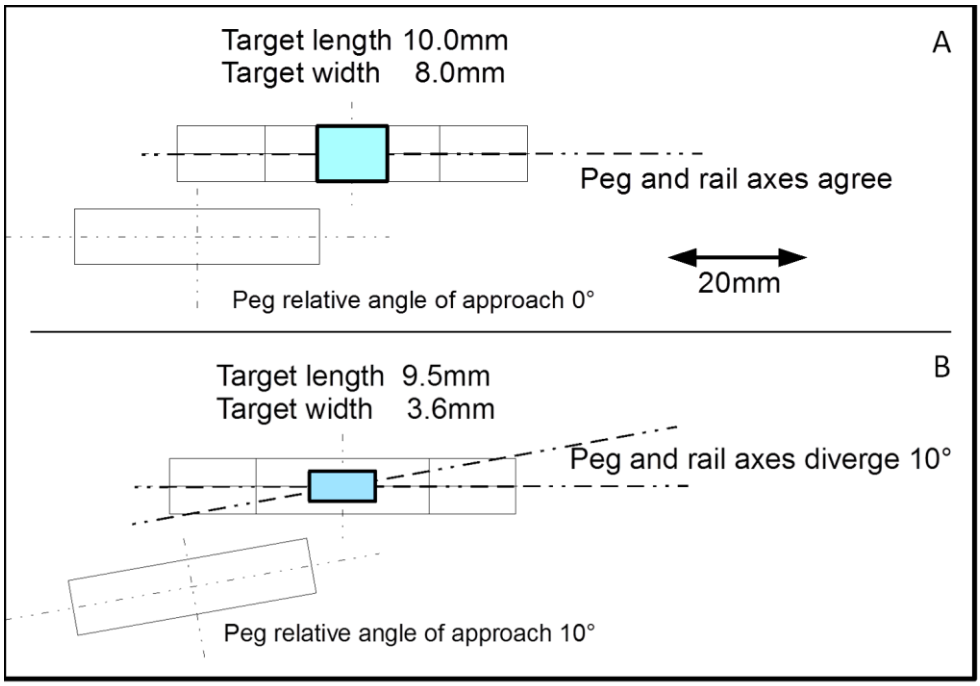


Figure 2.5: Effect of mismatch between rail and peg axes on effective target size

Effective target size is governed by the interaction between peg and receiver rail geometries. The geometric centre of the peg (intersection of centre lines) must lie within the bounds of the effective target size (blue rectangle) at release in order to sit across both raised areas, the rest condition required for scoring of accurate placement. A) When longitudinal peg and rail axes agree, the target size is largest. B) as the relative axes diverge, the effective target size decreases. The greatest effect is on target width. As axis divergence exceeds approximately 17.5° the effective target width tends to 0 as length tends to 8.3mm

Descriptives			
Fixed parameters	**symbol**	**dim**	**unit**
distance between raised rail supports	D	25	mm
rail width	W	8	mm
peg length	P	35	mm
Independent variable			
Relative difference between rail and peg longitudinal axes	α		°
Dependents			
effective target			
length	L		mm
width	y		mm
area	A		mm^2

Functions for all cases of α

L = D-(cosα*P)

y =W-(tanα*D)

A=L*y

Figure 2.6: Descriptives and functions describing the relationship between rail/peg axis differential and effective target dimensions.

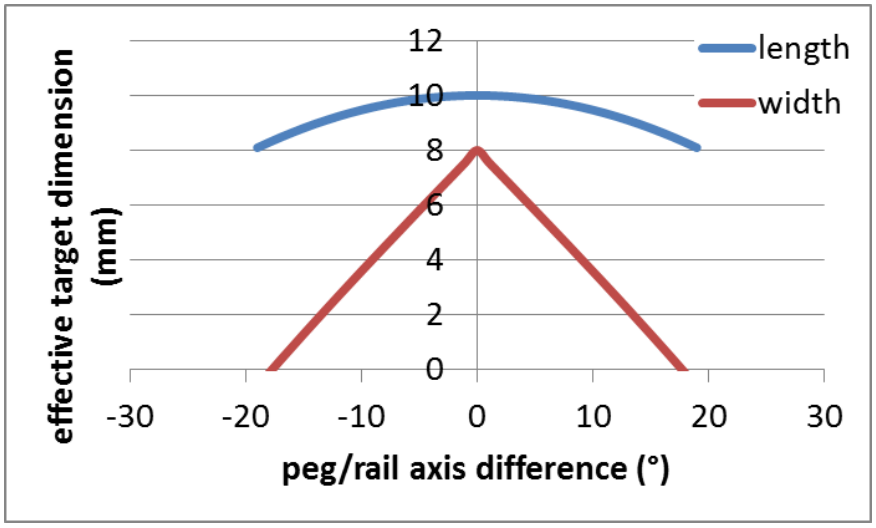


Figure 2.7: The effect on effective target length and width,of varying peg/rail axis angle differential.

Increasing the longitudinal angle differential has a near-linear relationship with effective target width, while the relationship with effective target length is curvi-linear. Effective width tends to 0 at 17.74° angular differential, when effective target length is still 8.40mm.

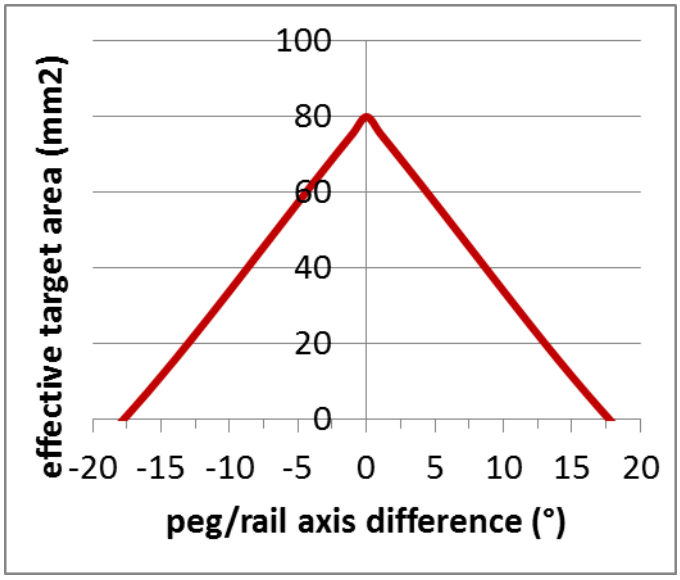


Figure 2.8: The effect on effective target area,of varying peg/rail axis angle at release.

The relationship between angle differential between peg and rail axes at the instant of peg release is directly proportional to the effective target area and is near-linear.

2.9.4 MSRT apparatus, generic measurement protocol and TPR calculation procedures

2.9.4.1 Introduction

We specifically wished to capture states of upper limb function in healthy persons and in iSCI tetraplegic persons up to the fifth cervical neurological level (Graves, Frankiewicz and Donovan, 2006) . The MSRT was designed to accommodate deficits in grasp and wrist strength and elbow extensor muscles but with preserved elbow flexion and shoulder control, similar to the psychometric characteristics of the Grooved Pegboard Test (Yancosek and Howell, 2009). This task incorporates a rotational element which in healthy persons depends heavily upon grasp adaptation. However rotational changes in the transverse plane may also be effected using compensatory movements of the glenohumeral joint and scapular elements of the shoulder girdle to develop alternative movement synergies (Hoffmann *et al.*, 2006). Grasp deficits may be addressed using a tenodesis action where wrist extensor function is sufficient to grasp lightweight objects (de los Reyes-Guzman *et al.*, 2010) providing tetraplegic persons with a range of alternative goal-directed strategic solutions to the task challenge (Koshland, Galloway and Farley, 2005).

Motor strength deficits were controlled for by selection of materials to minimise the weight and texture of moving test components. The reaching space and placement of the task were also respectively constrained in order to control for known variable impairments in reaching distance and cross-midline movement in tetraplegic persons (Robinson *et al.*, 2010). Following the general principles underpinning valid outcome measures (van Tuijl, Janssen-Potten et al. 2002) the MSRT also incorporates a well-defined start and end point and objective measure of task duration, as these time points are defined by participant operation of the start/stop button.

2.9.4.2 Development of behavioural measurement system

The justification for and development of the TPR outcome measure and MSRT task are discussed in Section VII.2.9.1.

2.9.4.3 Hardware and software requirements and setting up of the apparatus

The custom-made MSRT apparatus comes complete with 10 hardwood pegs each of cylindrical dimension 8 x 35mm. The on/off trigger switch on the task assembly (JellyBean Twist, art.

4088, Inclusive Technology Ltd., Oldham OL3 5FZ, UK) jack-plugs via a Simple Switch Adaptor (Inclusive Simple Switch Box, art. 3208, Inclusive Technology Ltd). This in turn plugged directly into the USB port of a computer running Windows software and with program Office Excel 2007 onwards available. A freeware stopwatch application was utilised as an add-in for Excel (Filho, 2012).The layout of the apparatus during each study was as shown in Figure 2.9.

Each participant was assigned a randomised non-repeating 5 element motor sequence coding which remained unchanged for the duration of participation in each study. The coding dictated the rotational angle of the 5 element MSRT rail array, each angle of which stipulated geometric target matching limits which resulted in a scaling of target difficulty. The investigator set the angles of the rail targets by lifting up the rail board and adjusting each rail fixer and orientation appropriately (Figure 2.10).

An Error Log sheet was also designed for recording of any errors occurring during task completion (detail, Figure 2.13). The Error log was a paper-based record which provided for the logging of the number and the position of errors within the rail array as they occurred (Figure 2.13) for later analysis.

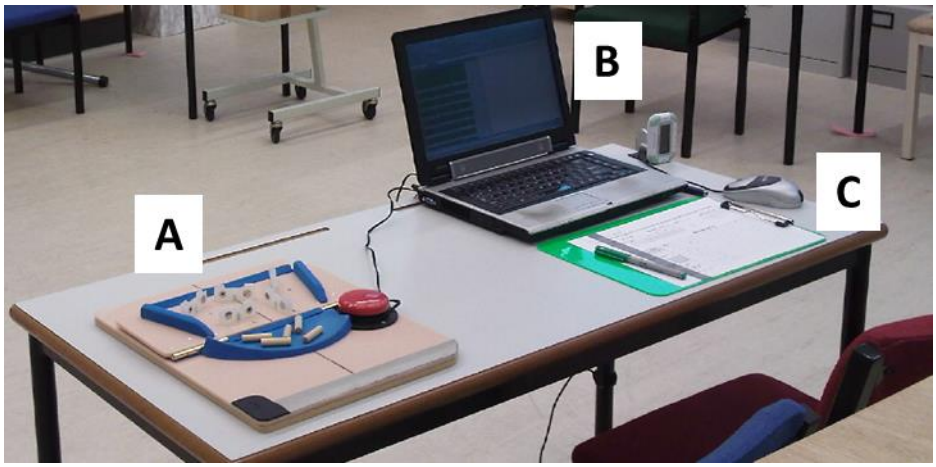


Figure 2.9: Layout of the MSRT apparatus for left-handed training.

The participant was seated with the MSRT apparatus (A) to the front. The MSRT start/stop button was linked to the computer (B) via a switch box and USB link. The investigator sat to the right of the participant, which provided for good surveillance of performance and physical access to reset the task without physically disturbing the participant. Resetting of the stopwatch via the computer mouse, and administration of the error log (C) was carried out by the same investigator.

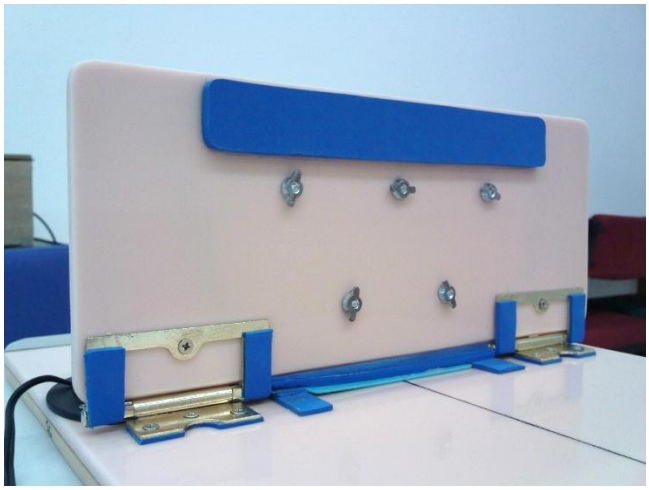


Figure 2.10: Rail board lifted to show the butterfly nut fixers retaining each rail target in place.

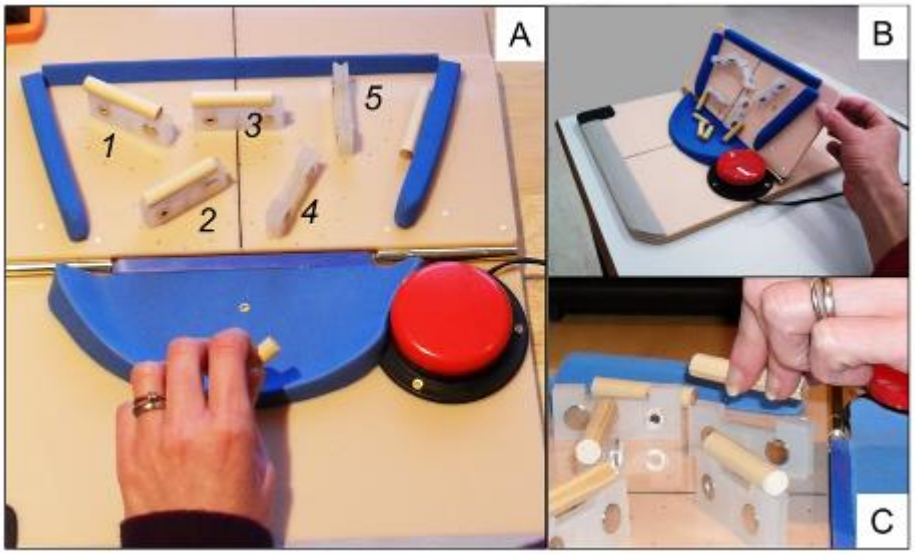


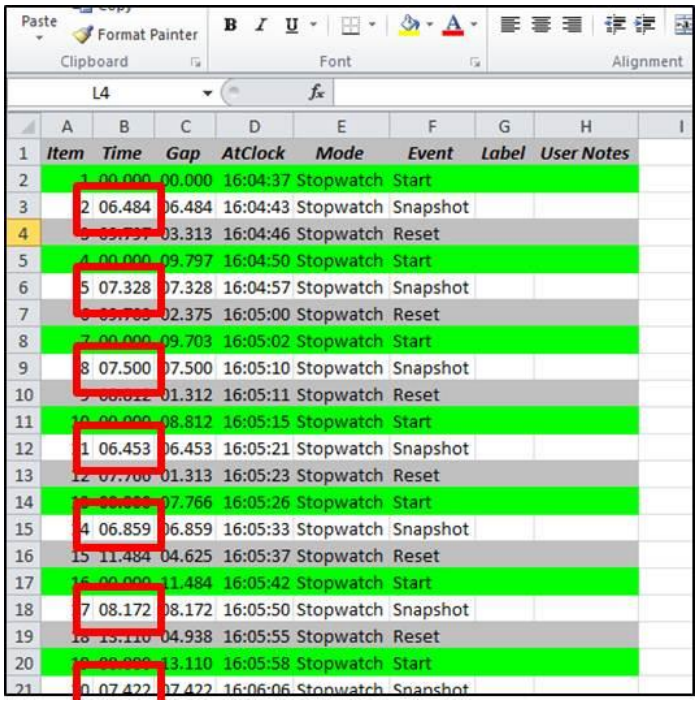
Figure 2.11: Motor Skill Rehabilitation Task (MSRT) procedure.

All activities were carried out with respect to the left upper limb. A) Rail angles were adjusted for each participant: illustrated are orientation angles 120°, 60°, 90°, 30° and 0° with respect to the centre line of the apparatus (black line) which was itself aligned to the left acromion process of the shoulder. Trial procedure: The participant triggered the start of the trial by tapping the start/stop button. Pegs were grasped from the dish and placed on rail targets in consecutive order from left to right (1 through 5). The start/stop button was tapped once more to end the trial. B) The investigator tilted the rail mounting board to return the pegs to the receiver dish in pseudo-random orientation. C) Detail of rail and peg placement. Rails were engineered with a longitudinal groove to securely capture correctly-placed pegs, and a central recession limits the effective target footprint dependent upon relative orientation angle. An error was scored if a peg failed to retain contact with the upper surface of both raised rail areas following release.

The board was placed on a desk table with the front of the board aligned with the edge of the table and the midline of the board aligned with the centre of the left shoulder joint (acromion process). 5 pegs were placed ready in the dish. The investigator sat to the right side of the task apparatus - this provided for good vision of the procedure, easy resetting of the task and independent administration of both computer-based and paper-based recording activities with the right hand (Figure 2.9).

2.9.4.4 Task administration

The MSRT task was administered according to the standardised instruction (Appendix B). During ongoing MSRT practise, repeated operation of the stopwatch button at the start and end of each trial generated a spreadsheet output (Figure 2.12) while the investigator recorded any errors on the Log sheet (Figure 2.13). Practise was carried out in blocks of 10 or 20 trials spaced by rests of approximately 1 minute.



	A	B	C	D	E	F	G	H	I
1	*Item*	*Time*	*Gap*	*AtClock*	*Mode*	*Event*	*Label*	*User Notes*	
2			00.000	16:04:37	Stopwatch	Start			
3		06.484	06.484	16:04:43	Stopwatch	Snapshot			
4			03.313	16:04:46	Stopwatch	Reset			
5			09.797	16:04:50	Stopwatch	Start			
6		07.328	07.328	16:04:57	Stopwatch	Snapshot			
7			02.375	16:05:00	Stopwatch	Reset			
8			09.703	16:05:02	Stopwatch	Start			
9		07.500	07.500	16:05:10	Stopwatch	Snapshot			
10			01.312	16:05:11	Stopwatch	Reset			
11			08.812	16:05:15	Stopwatch	Start			
12		06.453	06.453	16:05:21	Stopwatch	Snapshot			
13			01.313	16:05:23	Stopwatch	Reset			
14			07.766	16:05:26	Stopwatch	Start			
15		06.859	06.859	16:05:33	Stopwatch	Snapshot			
16		11.484	04.625	16:05:37	Stopwatch	Reset			
17			11.484	16:05:42	Stopwatch	Start			
18		08.172	08.172	16:05:50	Stopwatch	Snapshot			
19			04.938	16:05:55	Stopwatch	Reset			
20			13.110	16:05:58	Stopwatch	Start			
21		07.422	07.422	16:06:06	Stopwatch	Snapshot			

Figure 2.12: Screenshot of MSRT time completion record.

Red rectangles: completion time score results were drawn from white-coloured 'snapshot' rows in the 'Time' column. Green 'start' row: trial initiated by a touch on the MSRT assembly start/stop button. White 'snapshot' row: triggered by a second touch on the start/stop button, indicating the end of the trial. Unintentional snapshot triggers during a trial were noted and filtered during later processing. Grey 'reset' row: the investigator reset the stopwatch function in preparation for the next trial.

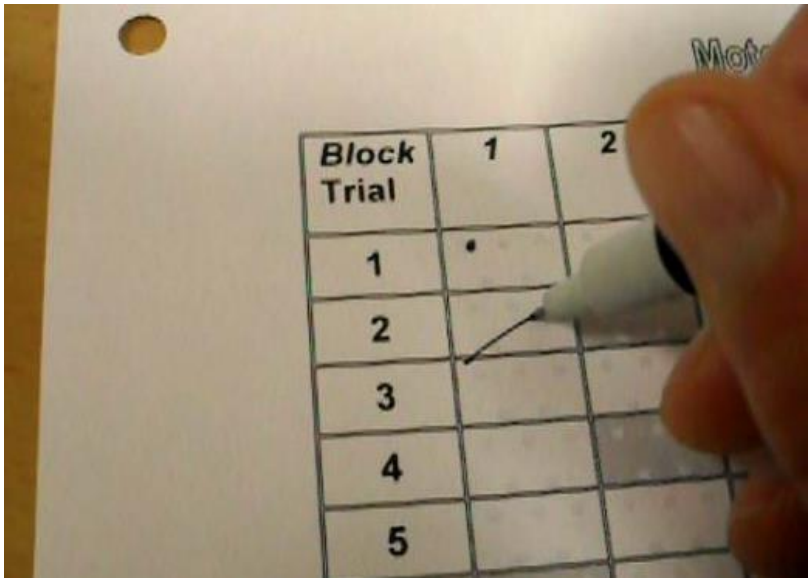


Figure 2.13: Method of logging spatial error.

The errors/accuracy sequence was logged during the task sequence. Errors were marked, with accurate placements left unmarked. Clear trials were struck through for clarity. These sequences were later united with the corresponding record of completion time.

2.9.4.5 MSRT trial sampling protocols

TPR samples were averaged as arithmetic means across a fixed number of trials or a fixed duration of task experience, as dictated by the trial objectives and the target population of each study.

The premise for the MSRT outcome measure is firstly that, in behaving humans (Jensen, Marstrand and Nielsen, 2005b) and non-human mammals (Remple *et al.*, 2001) the capacity to learn motor skills can be disassociated from physiological parameters influencing manual strength, of which joint velocity is a direct function. Secondly, it is recognised that task-dependent skill is an unstable construct and is a parameter altered by and during the measurement process. Thirdly, learning is experience-dependent (Warraich and Kleim, 2010) and therefore tied to performance and exposure time rather than arbitrary numbers of trial repetitions (Eliassen, Souza and Sanes, 2003).

It is common practise to summarise motor outcomes over a number of trials. When the sample is fairly homogenous across physiological variables and task completion times are similar across the sample population, there is little material difference between these sampling approaches. A problem arises when the population is heterogeneous between-subjects for strength capacities. In general, stronger individuals are likely to develop higher positive and negative joint velocities in reaching between fixed points and it is self-evident that stronger

individuals might complete more trials of a given training task within a given dosage period of continuous practise. Thus, if we wish to avoid any instrument bias while capturing a skilled performance in a repetitive sequential task outcome then the standardised interval might best be fixed over time rather than over a fixed number of trials.

The MSRT is implemented in Study 1 and Study 3 which include healthy samples, and for convenience an arbitrary number of trials constituted a sampling interval. In Study 2, the incomplete SCI sample was heterogeneous for sparing of motor and sensory functions and the number of task trials completed during each training session differed markedly between volunteers. During the pilot study, task practise was therefore sampled from MSRT trial performances corresponding as closely as possible to a fixed time period.

2.9.4.6 Processing of task completion time and error data to TPR outcome

The task completion time scores were filtered and converted into number format. The corresponding error score for each trial was entered into a separate column on the same spreadsheet row as the corresponding task completion time. The TPR score was then calculated as the completion time for each individual trial divided by the residual number of accurate placements n = (5 – errors recorded) achieved during that trial (Equation 2.9-1), to provide a parsimonious measure of goal-oriented motor capacity over the sampling period.

$$TPR = \frac{completiontime(s)}{residualaccuracyscore(n)} \left({}^{s}/_{score}\right)$$

Equation 2.9-1: Task Productivity Rate (TPR), derived arithmetically from time score and residual accuracy score.

For example, completing a trial in t=5.000s, 1 incurred error gives a residual accuracy score of *n*= 4. The TPR = *t/n* = 5.000/4 = 1.25 s/score.

2.9.4.7 Treatment of task errors and outliers

Strict rules were applied in order to avoid gathering data which was atypical of normal performance within the constrained workspace of the apparatus. Only trials containing the following errors were excluded from analysis, to ensure that qualitative considerations on the part of the investigator did not lead to measurement bias. If these errors occurred, the trial was stopped and the task reset. Additional trials were be completed to bring the number of valid trials to the desired N number of trials per block.

- Handling errors: occasionally, participants made a grasping error causing a peg to fall outside the area of the apparatus board.
- Mechanical errors: the mechanical start/stopwatch button switch operated under light pressure (25g static load). Failure to trigger software operation typically occurred less than once in approximately 200 operations.

2.9.4.8 Sensitivity limits and resolution of the error score

The sequential motor task, including an array of dimensionally similar targets was ideally made up of a number of similar spatial elementary subtask actions and therefore by definition, accuracy in the conceptualised task was spatially constrained to a degree dependent upon the design parameters of the target and peg (Figure 2.6). Whether or not accurate placements were made it was reasoned that the participant made valid *attempts* (otherwise the trial would be invalid and the investigator must reject the result of the trial from the dataset). So if, following a trial the spatial outcome was an accuracy score of 0, we would have no information to show that performance did *not* tend towards one accurate placement on at least one of the targets. Then logically, the true accuracy was more likely to approach 1 than 0 of 5 possible target placements per trial.

Hence, in scoring a trial where no accurate peg placements occurred we would have assumed that the participant was nearly successful in achieving one targeting goal, but assigned the score across the target array (a score of 0.2 per target, totalling 1 across the array) on the basis of equal probability. Equally, it was recognised that this constituted a floor effect in relation to the error score.

In practise, this floor effect was not observed at any time during the project.

2.9.4.9 Task administration instructions

See Appendix B.

2.10 Validated functional measures of upper limb dexterity

Lesions of the cervical spinal cord often lead to incomplete impairments of upper limb function. Patients consider the reinstatement of upper limb function to be amongst their highest rehabilitation priorities (Snoek *et al.*, 2004; Hanson and Franklin, 1976) in order to take an active part in daily activities (Mulcahey, Hutchinson and Kozin, 2007). In order to accurately assess and track states of ability, measurements should include validated tests of arm-hand function (Yancosek and Howell, 2009). Suitable tests should be sensitive to change, require complex repetitions of the joints of the upper limb, and have clear start and end points (van Tuijl, Janssen-Potten and Seelen, 2002). The following measurements were selected because they have previously been evaluated in depth in healthy and patient populations and the outcomes derived believed to reflect aspects of upper limb function.

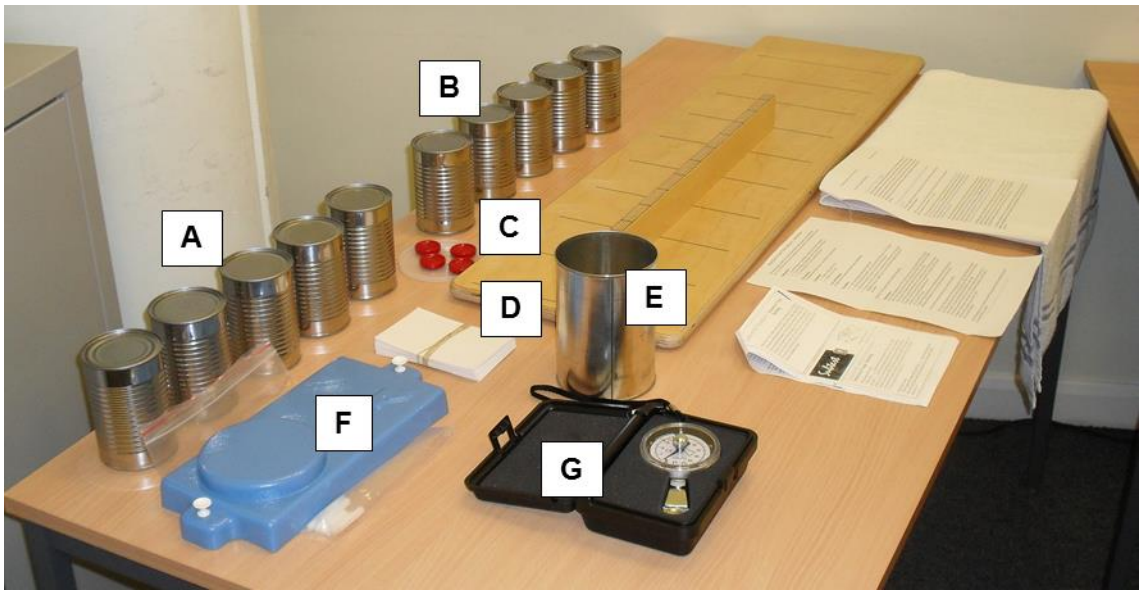


Figure 2.14: Validated functional tests and measures.

A-E: subtests of the Jebsen Taylor Hand Function Test battery in order, light/heavy cans, checkers, card turning, small objects. F: 9 hole peg test apparatus. G: Pinch force gauge.

2.10.1 Nine-hole peg test (9HPT) (Kellor *et al.*, 1971).

The 9HPT was selected as a behavioural outcome measure for Study 2.

The recommended criteria for the application of outcome measures in tetraplegics include fast administration time, sensitivity to the extent of disability and time-dependent changes (Mulcahey, Hutchinson and Kozin, 2007). The purpose of outcome measurement in this study is to establish the relative efficacy of anodal tDCS rehabilitation of skill/dexterity in the non-

dominant hand. Peg tests are often used to evaluate the outcome of studies focusing on changes in hand function (Langhorne, Coupar and Pollock, 2009). The 9HPT was selected as a validated instrument which specifically reflects levels of dexterity in the healthy or impaired hand (van Tuijl, Janssen-Potten and Seelen, 2002).

The 9HPT is a commonly-used (Oxford Grice *et al.*, 2003) non-disease specific measurement of fine motor dexterity which is quick and simple to apply (Olindo *et al.*, 2008). This has good inter-rater reliability (IRR) r=0.99 with regard to the left hand though moderate test-retest reliability (TRR) r=0.43 ((Mathiowetz *et al.*, 1985) in (van Tuijl, Janssen-Potten and Seelen, 2002)). Moderate concurrent validity with another functional test of dexterity, the Purdue Peg Test (r=-0.53) was also demonstrated.

The test has been evaluated for reliability in several dexterity-impaired groups. In 62 stroke patients, 62% of whom had detectable spasticity in the more affected hand, Chen et al. (2009) found that, based on the mean of 3 repetitions applied several days apart, the TRR as indicated by the intraclass coefficient was mean 0.85 on the more affected side and 0.89 on the less affected side indicating good reproducibility (t-test values for the difference $p>0.4$). Within-sessions scoring variability indicated by the standard deviation was, however high, again indicating the need for multiple trials, while reduced reliability was associated with spasticity in the more affected hand (Chen *et al.*, 2009).

Heller et al (1985) found the 9HPT more sensitive to change compared to the Frenchay arm test in sub-acute stroke patients, particularly in those demonstrating greater dexterity in ADL tests, although there may be a floor effect when applied to those with the poorest functional abilities (Heller *et al.*, 1987), a finding concurrent with those of of Chen et al. (2009) and Sutherland et al. (1989). Sensation must be important in giving rise to this floor effect (Sunderland *et al.*, 1989) and as such, an important factor in manipulation of objects.

Corben et al. (2009) assessed the responsiveness to changes over time of 3-trail average 9HPT scores alongside the Jebsen Taylor Hand Function Test (JTHFT) and the Box and Block Test (BBT) in a 38-strong cohort drawn from the Friedrichs Ataxia (FA) population. The 9HPT gave the largest effect size, suggesting the greatest sensitivity of the three tests for changes occurring in the non-dominant limb, 95% CI = -0.0009 (-0.0016, -0.0002) p=0.02, minimising the sample size that would be required to show a significant change in the level of dexterity in a similarly powered study (Corben *et al.*, 2009).

The 9HPT has not recently been formally evaluated in the population of interest but it has been investigated in healthy and dexterity-impaired groups and found to be a sensitive, reliable and valid outcome measure which is simple, portable and easy to apply. The measure has been promoted as the most suitable upper limb outcome to detect changes in MS (Rosti-Otajarvi *et al.*, 2008) FA (Corben *et al.*, 2009) and CSM (Olindo *et al.*, 2008) patient groups. Studies have been carried out in adults 8 to 71+ and there is a broad agreement of findings across the studies discussed. There is the proviso that the mean values of multiple trials should be used to provide data with good TRR.

A Rolyan 9HPT standardised apparatus and administration instruction (Art. A851-5, Homecraft Rolyan NG17 2HU, UK) was used during this project.

2.10.2 Jebsen Taylor Hand Function Test (JTHFT) (Jebsen *et al.*, 1969)

This generic test of hand function was selected as a secondary behavioural outcome measures in Studies 3 and 4.

The JTHFT was developed and has been widely used to assess the extent of hand disability and broad functional changes due to therapeutic intervention (Mulcahey, Hutchinson and Kozin, 2007; van Tuijl, Janssen-Potten and Seelen, 2002). The JTHFT is considered valid for use with SCI subjects (van Tuijl, Janssen-Potten and Seelen, 2002) and has been used to show significant improvements in incomplete SCI hand function following massed practise and median nerve stimulation (Beekhuizen and Field-Fote, 2008; Hoffman and Field-Fote, 2007) and tendon transfer (Colyer and Kappelman, 1981).

The JTHFT has previously been applied as an outcome measure in the behavioural study of tDCS effects on motor function in healthy subjects (Boggio *et al.*, 2006a; Hummel *et al.*, 2010; Hummel and Cohen, 2006) and patients (Boggio *et al.*, 2007; Hummel *et al.*, 2005). Patient groups TRR in stable hand disorders has been reported as high: r=0.89 to 0.99 except for the writing subtest (r=0.67) and the simulated feeding subtest (r=0.60) in the non-dominant hand (Jebsen et al. (1969) in Van Tuijl et al. (2002)) a feature also noted by Stern et al. (1992).

Blennerhassett et al. (2008) showed that in stroke patients, the ability to control pinch grip force for prehension/lift sequencing correlated strongly with the combined small-object and checker-stacking time-score ($r = 0.78$, $p<0.01$) (Blennerhassett, Carey and Matyas, 2008). This

result is indicative of the sensitivity of JTHFT subtests to changes in dexterity, which were not significantly different between dominant and non-dominant stroke-affected hands. Furthermore, the small-object subset was also sufficiently sensitive to detect early improvements in dexterity using either hand $p<0.01$, following posterior decompression surgery in CSM patients (Prabhu *et al.*, 2005). Because the JTHFT evaluates functional grasp activities, a floor effect may exist and limits the utility of this outcome to studies of residual grasp ability (Blennerhassett, Carey and Matyas, 2008) rather than simple active movement (Prabhu *et al.*, 2005).

A standardised JTHFT apparatus and administration instruction (Art.09-103-0501, Homecraft Roylan, UK) was used throughout this project. Writing and feeding subtests were not included, on the grounds that the reliability of these tests has been questioned (Stern, 1992) and, furthermore, that those tasks are arguably not contextually relevant to the non-dominant hand.

2.10.3 Pinch force

Pinch force was used as a functional outcome measure in Study 2.

Using a standardised testing protocol and multiple test trials and intertrial periods of 3-5s and 15-60s respectively (Sisto and Dyson-Hudson, 2007) instrumented strength testing has been shown to be more reliable than manual muscle testing (Larsson *et al.*, 2003; Herbison *et al.*, 1996; Schwartz *et al.*, 1992). Muscles must possess a Oxford scale strength grading of 3 out of 5 or greater for dynamometry to be useful as an outcome measure (van Tuijl, Janssen-Potten and Seelen, 2002; Schwartz *et al.*, 1992).

Strength deficits impair the ability of individuals with SCI to perform ADL (Sisto and Dyson-Hudson, 2007) a relationship particularly relevant in tetraplegia (Noreau *et al.*, 1993). Pinch force is a clinically important parameter of upper limb function in recovery from tetraplegia (Hamou *et al.*, 2009) and stroke (Blennerhassett, Carey and Matyas, 2008; Hummel *et al.*, 2006). Anodal tDCS has been shown to enhance maximal voluntary contraction force (Tanaka *et al.*, 2009) and stamina (Cogiamanian *et al.*, 2007) in the short term. Previous studies in the lower limb have indicated a transient facilitation of pinch force after focal stimulation with anodal tDCS to the leg cortical representation of the non-dominant M1(Tanaka *et al.*, 2009), which might indicate either short-term facilitation of corticospinal drive or kinematic refinement (Tanaka *et al.*, 2009) and itself suggest an enhanced learning effect. However, in an investigation of neuromuscular fatigue upon elbow flexors, Cogiamanain *et al* (2007) found no

facilitation of maximum voluntary contraction (MVC) but a significant improvement in fatigue-resistance after anodal tDCS. It was therefore considered of interest to investigate this phenomenon in tetraplegic persons, by assessing MVC lateral grip pinch force before and after each session. A JAMAR-type hydraulic hand-held pinch force dynamometer was used (Art. SH5005, Saehan Corp. PO Box 426 Republic of Korea). This apparatus is supplied with a standardised instruction.

Figure 2.15: Standardised positioning for measurement of pinch force.

The investigator held the JAMAR-type pinch force dynamometer in position while the participant produced a 5-second maximum effort.

2.11 Anodal tDCS

Practical, generic equipment considerations and procedures for application of tDCS modalities have recently been summarised in a useful guidance paper (DaSilva *et al.*, 2011).

2.11.1 Hardware

A ramp-controlled battery driven stimulator (CX-6650, Rolf Schneider Electronic, Gleichen D-37130, Germany, datasheet Appendix A) was utilised in all cases for delivery of the intervention in the current project. During the single blinded pilot study the stimulator unit was concealed from the vision of participants and manually operated by the investigator. Double blinding of both the investigator and participants to group allocation was assured in the definitive Study 3 by securing the unit in a locked box and using the semi-automated procedure detailed at (VII.2.11.4.)

Current was applied from the unit via flying leads from the stimulator to rubberised electrodes, which in turn were sheathed in rectangular sponge electrode pads of area 35cm^2. Each pad was well-soaked with 1% saline solution before placement on the scalp to ensure good conductivity for the safety and comfort of participants (Loo *et al.*, 2011; Dundas, Thickbroom and Mastaglia, 2007).

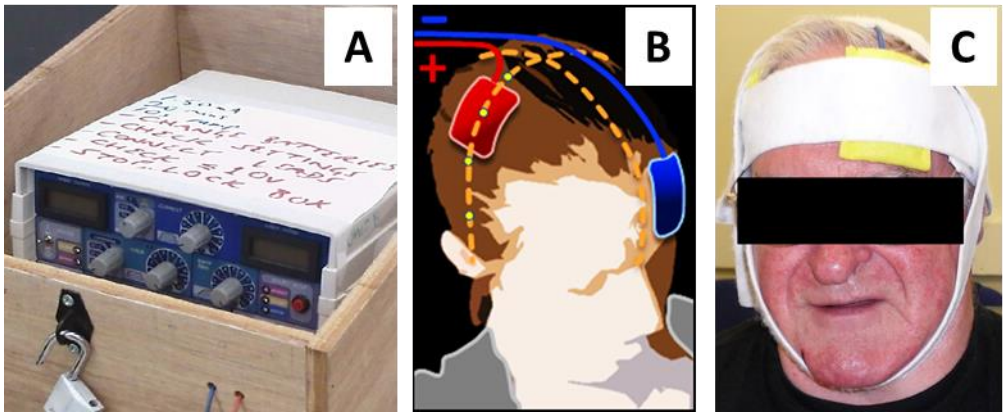


Figure 2.16: Anodal tDCS hardware and application

A: Anodal tDCS stimulation was delivered from a battery driven constant current DC stimulator. For Study 3 the stimulator unit was secured in a locked box as illustrated and actuated remotely for the purposes of double blinding B: Standardised electrode pad placement: anode (+) placed overlying the right M1 region (area C4, 10-20 system), reference electrode (-) placed superior to the contralateral orbit. C: Practical application in an experimental subject, with saline-soaked pads secured via elasticated strapping.

2.11.2 Stimulation parameters and safety considerations

During each of 2 training sessions healthy participants, who took part in the definitive Study 3 received 1.5mA direct current (DC) at steady state voltage 10V or less with the current ramped up/down over 10 seconds at the onset and completion of stimulation respectively. Tetraplegic patient who took part in Study 2, and undertook 3 sessions of training on consecutive days received 1.0mA DC stimulation. Both current intensities are within accepted limits for safety (Liebetanz *et al.*, 2009), comfort (Dundas, Thickbroom and Mastaglia, 2007) and blinding (Gandiga *et al.*, 2006). The lower value was applied as an ethical consideration because this patient group was not known to have previously been exposed to tDCS stimulation, and in view of the application of the intervention on 3 consecutive days which might have a cumulative effect upon humans. For example, a low incidence of skin burns to the surface of the scalp has been previously reported during repeated session tDCS stimulation protocols (Frank *et al.*, 2010; Palm *et al.*, 2008), and so we also took care to clean and regularly replace sponge pads, use fresh saline conductive solutions and carefully inspect the skin areas for damage prior to pad placement (Frank *et al.*, 2010). Compared to the literature, both of these amplitudes fall into a moderate amplitude range (Jacobson, Koslowsky and Lavidor, 2012; Nitsche *et al.*, 2008; Poreisz *et al.*, 2007) and the duration of stimulation was as applied in

previous protocols (Jacobson, Koslowsky and Lavidor, 2012; Loo *et al.*, 2011) in conjunction with a standardised electrode pad size and conductive solution.

After initial pad placement the DC stimulator was switched on for 30 seconds until the voltage had stabilised. If the voltage was greater than 10V, suggestive of high resistance and therefore a propensity to heating under the pad area (Palm *et al.*, 2008), or if the participant reported discomfort the fitting of the electrode pads was checked and adjusted as necessary and this procedure repeated until these criteria were satisfactory.

The possible effect of physical variables have been considered by others, not only in relation to the size and shape of the electrode pads (Datta, Elwassif and Bikson, 2009; Datta *et al.*, 2009) but also in relation to the effects relating to the positioning of the cathodal electrode (Nitsche *et al.*, 2008). Other cephalic and non-cephalic 'reference' electrode positioning montages have been used previously but the position utilised in the current project is preferable, not only because the effect of tDCS on MEPs is inversely proportional to the distance between the electrodes (Moliadze, Antal and Paulus, 2010) but also in order to reduce shunting of current through superficial tissues, which would reduce the strength of the electric field acting through the brain (Nitsche *et al.*, 2008). Furthermore, the excitation effect of electrical fields thought to underlie plastic changes associated with learning is sensitive to dendrite-axon orientation, which could be affected by electrode placement (Radman *et al.*, 2009; Roth, 1994).

However, although the current project is focused upon effects associated with the placement of the anodal electrode, the cathodal electrode is also active and is known to cause short-lasting reductions in excitability in neurons underlying the site of the electrode (Nitsche and Paulus, 2000). When tDCS is applied to the frontal cortices it is thought to be safe (Nitsche *et al.*, 2004) and is in general considered as not relevant to findings in respect of motor performance (Nitsche *et al.*, 2008). But, though such investigations lie outside the scope of the current project and do not affect the validity of the findings, the implications of excitability reductions over the frontal cortices electrodes might be considered as a number of distributed, high-level cognitive processes including motivation and executive functions are supported across the frontal regions (Stuss, 2011a; Stuss, 2011b).

2.11.3 Application of anodal tDCS for stimulation of the non-dominant M1

Pads were secured in place with elasticated strapping and remained in place for the entire duration of training sessions (Figure 2.16c).The method for identification of scalp surface points according to the standards of the International 10–20 EEG System (Klem *et al.*, 1999) has been described in detail (Milnik, 2009). the active pad (anode) was consistently applied over the C4 area overlying the non-dominant (right-side) primary M1 according to the 10-20 EEG system (Herwig, Satrapi and Schonfeldt-Lecuona, 2003) with the reference pad applied over the contralateral supraorbital ridge (Figure 2.16b).The intervention was delivered to those receiving ACTIVE stimulation for 20 minutes continuously, starting simultaneously with the start of task practise. For all studies, the DC stimulator was automated for a current duration of 20 minutes, including ramping up and down over a 10 second period.

During the Study 2the SHAM group received stimulation for 45 seconds both at the start and end of a 20 minute period. This pattern of stimulation created procedural difficulties in maintaining the level of blinding in the the definitive study, therefore the protocol was altered for Study 3so that the SHAM group received stimulation for approximately 45 seconds both at the start of training only. Both of these approaches have been applied in previous tDCS studies with no apparent quantitative difference in the results.

2.11.4 Arbitrary placement of scalp electrodes for application of anodal tDCS at the non-dominant primary M1

The method of, and validity for, the method for identifying cortical loci using the international 10-20 EEG system (Klem *et al.*, 1999)has been well-described (Milnik, 2009; Okamoto *et al.*, 2004; Herwig, Satrapi and Schonfeldt-Lecuona, 2003). The 10-20 system has been utilised for arbitrary electrode pad placement in a number of tDCS behavioural/neurophysiological studies (Hesse *et al.*, 2007; Fregni *et al.*, 2006b; Iyer *et al.*, 2005; Boros *et al.*, 2008).

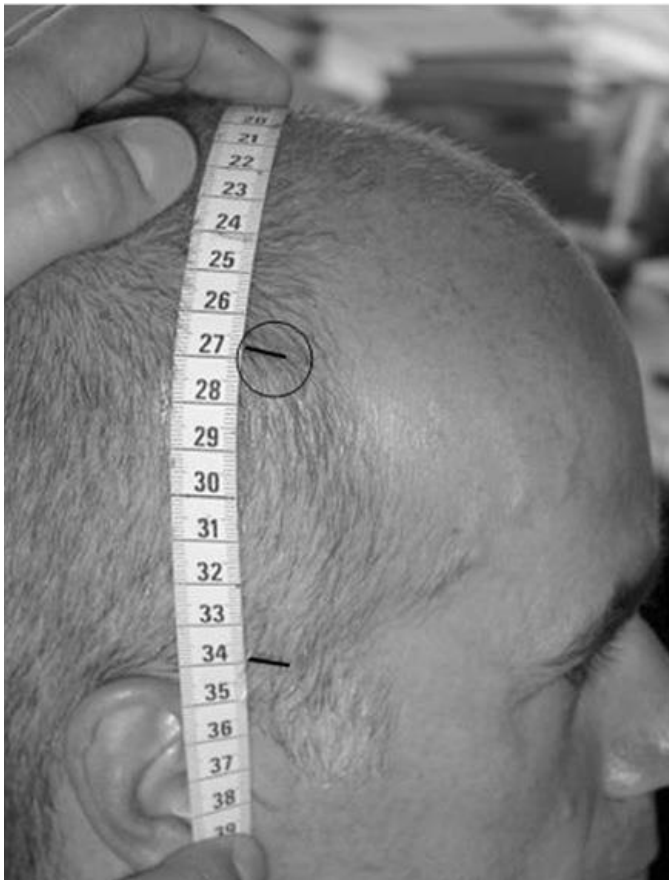


Figure 2.17: Area C4 identified from surface measurement.

Area C4 (circled) is identified as 40% of the distance between the measured vertex of the head (Cz) and the tragus of the ear. From (Milnik, 2009).

In a study sample of 10 healthy subjects assessing the relative discrepancy between different noninvasive methods for localisation of brain regions (Sparing *et al.*, 2008) Sparing et al. (2008) found a mean anterior deviation of the centre of gravity for maximum TMS-evoked MEP (at flexor digitorum indicus) relative to C3 with Cartesian deviation 12.3mm ± standard deviation 4.4mm, range 2-21mm. The dominant component of this deviation was in the sagittal plane (Sparing *et al.*, 2008). In studies involving cortical mapping, the primary motor cortical maps of spinal injured subjects have been shown as shifted posteriorly and attenuated (Jurkiewicz *et al.*, 2010; Green *et al.*, 1998) relative to those of healthy individuals, perhaps of the order of 15mm (Hoffman and Field-Fote, 2007) and which might evolve over time (Lotze, Laubis-Herrmann and Topka, 2006). Spontaneous sensorimotor recovery (Jurkiewicz *et al.*, 2007) or

adjunctive neurorehabilitation intervention (Lynskey, Belanger and Jung, 2008; Hoffman and Field-Fote, 2007) can normalise the presentation towards the healthy control state over time.

Thus, while we recognise that considerable use- and/or intervention-dependent changes in the topography and excitability of specific motor representations may occur, any migration of cortical representations are likely to remain within the margins of the size of electrode pads to be used in the present study – that is, 50mm x 70mm, with the long axis extending laterally from the vertex. These dimensions are sufficiently large to cover the entire region of the scalp overlying right-side hand and arm area of M1 (C4).

The effects of tDCS are thought to be dependent upon cell morphology (Radman *et al.*, 2009) tissue architecture (Datta *et al.*, 2009; Nitsche and Paulus, 2000) and CSF conductivity (Datta *et al.*, 2009) which interact with the static electric field produced by DC stimulation (Nitsche and Paulus, 2000) rather than centralisation of electrode pads over stimulation loci. Indeed, authorities on this topic are circumspect on the subject of focality, advocating the utility of larger electrode pads to reduce variability of effects (Nitsche *et al.*, 2008) and it is recognised that one of the potential practical advantages of tDCS compared to other forms of non-invasive brain stimulation is the non-focality of application (Priori, Hallett and Rothwell, 2009). The non-focal nature of tDCS for stimulation when using large electrode pads of the proposed size provides for stimulation of the cortical representation of the entire non-dominant upper limb including the representation of the hand muscles. We consider, therefore, that the resolution offered by this convenient method of stimulation locus identification is adequate for application in tDCS studies. Furthermore, in a background study we found evidence which further supports this opinion in relation to multiple muscles of the upper limb (VII.2.12.1).

2.11.5 Assignment to groups, blinding to allocation and switching methods

Concealment of participants and investigators is important to minimise bias in experimental studies (Torgerson and Roberts, 1999) and random allocation aims to ensure no systematic differences exist in known and unknown factors that can affect the outcome (Sibbald and Roland, 1998). For both interventional studies, volunteers were allocated to groups on the basis of randomisation by pairs to maintain balanced data collection during ongoing, rolling recruitment. A practise of rolling recruitment was applied during all studies. The ordering of randomisation pairs was generated from a reputable, internet-based random integer generation service (Haahr and Haahr, 2012).

All activities during the pilot study involving patients were carried out on the NHS site by the lone researcher. There was neither skilled assistance nor the technological capacity for automated blindingavailable. For these reasons a single level of blinding the participants, but not the researcher to the group allocation was possible and ethical approvals were granted with that understanding.

The definitive study involving healthy persons took place in laboratory facilities within the School faculty, where assistance was available from School technical staff. Double blinding of both the investigator and participants to group allocation was assured in the definitive study by securing the unit in a locked box, with the DC stimulation unit switched remotely. A remote switching capability is included as a design feature on the CX-6650 stimulator model.

The signal software was programmed to deliver one of two routines on the basis of an X or Y key entry, initiated by a second assistant who entered a coding key (Figure 2.18). The designation of the coding key, either to active or sham intervention, was known only to a third party, the Academic Supervisor for the current project.

The switching routine for both groups was generated from a concealed Signal program routine running on a PC running Spike for Windows Software (Cambridge Electronic Design (CED), Cambridge CB4 0FE, UK), and outputted via a CED Micro1401Mk2 (CED, UK) 5 volt digital output channel. A rising-edge transistor-to-transistor logic (TTL) toggle on-off signal was transmitted via a bayonet connector interfaced, standardised radio frequency-shielded coaxial cable connection to an optically-isolated control input at the rear of the unit.

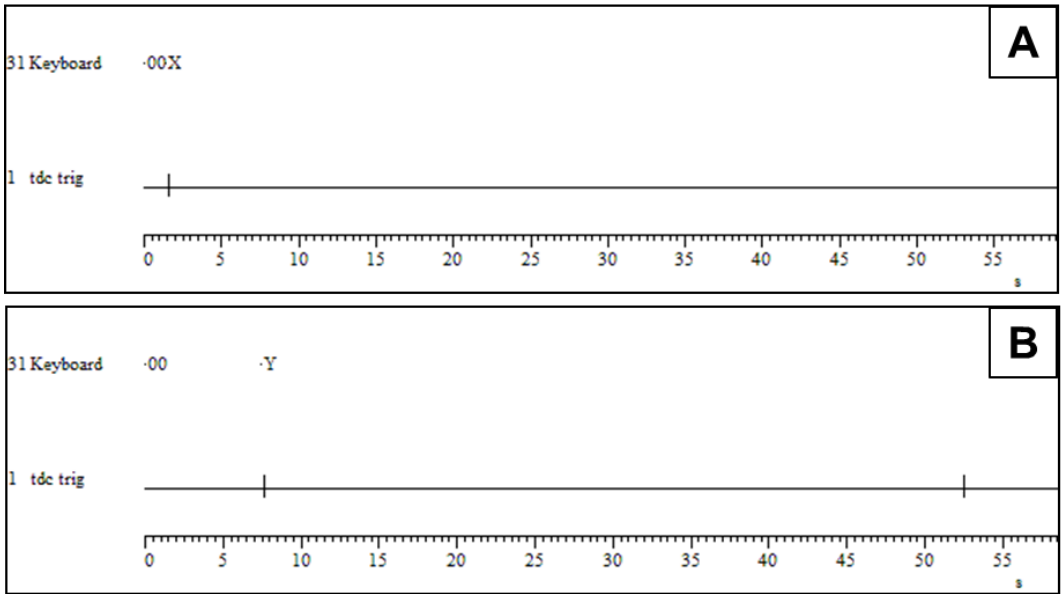


Figure 2.18: Signals for remote switching of DC stimulator during Study 3.

The switching signal for triggering of the DC stimulator unit was initiated by a coded entry via the PC keyboard. A: Active stimulation routine. A single trigger initates the stimulator unit after 2 seconds, with the unit set to cease stimulation after 20 minutes. B: Sham stimulation routine. On-trigger at 8 seconds, with off-trigger 45 seconds later.

2.12 TMS protocol validation, measurements and common protocols

The definitive study involved the application of TMS-evoked outcome measures. The background validation of TMS measurements and tDCS electrode placement, common use of hardware and software equipment, methods of preparation and equipment calibration, and application of standardised protocols is discussed in this section. Techniques and procedures specific to particular chapters are detailed in the relevant chapters.

2.12.1 TMS background study – confirmation of neurophysiological measurement protocol feasibility and arbitrary placement of tDCS stimulation pads

An ethically approved background study to the project was carried out between November 2009 and July 2010, which included 14 healthy volunteers. This had 2 objectives; firstly to investigate the feasibility of gathering stimulus-response curves (SRc) from representative proxima and distal arm muscles and secondly to map the representations of these muscle. This study found that non-dominant cortical representations were less excitable than dominant representations of homologous muscles, and proximal muscle representations were less excitable than those of distal muscles as found by others (Wassermann *et al.*, 1992). Resting threshold responses were not reliably elicited from proximal muscles in the resting state. But low-level muscle activation at 10% or 20% of maximal voluntary contraction (MVC) readily elicited active motor thresholds in proximal and distal muscles at levels low enough for facilitated stimulus-response recruitment curves (SRc) to be reliably gathered with a limited number of stimuli and over a standardised period of time, suggesting equivalence of reliability.

Mapping of the cortical representations of Abductor Pollicus Brevis (APB), Biceps Brachii (BB) and medial Deltoid (mDelt) muscles confirmed that as found previously(Devanne *et al.*, 2006)per hemisphere the area representations of proximal mDelt and distal APB muscles had closely adjacent loci and substantially overlapping excitability representations (Figure 2.19). These representations were, to a substantial extent sited within the 7x5cm margins of electrode pads centralised on position C4 of the 10-20 EEG system, with the long axis of the pad aligned mediolaterally (Figure 2.19). The position C4 is determined by measurement of the scalp in relation to points on the head and is highly repeatable in humans (see Section VII.2.11.4). While some tDCS studies utilise accurate placement techniques from MRI or TMS measurements of the area of greatest response from the cortical muscle representation

(Hummel *et al.*, 2010; Hunter *et al.*, 2009; Hummel *et al.*, 2005) others have used the arbitrary positions C3 and C4 of the 10-20 EEG system (Klem *et al.*, 1999) for the placement of tDCS electrode pads over the M1 region of interest (Hesse *et al.*, 2011; Vines, Cerruti and Schlaug, 2008; Hesse *et al.*, 2007; Fregni *et al.*, 2006b). We concluded that the method of arbitrary use of C4 for placement of 7x5cm electrode pads was practical and had validity for proximal as well as hand muscles.

These results informed the design of TMS measurement protocols and tDCS electrode pad placement positions during the experimental studies carried out in the current project.

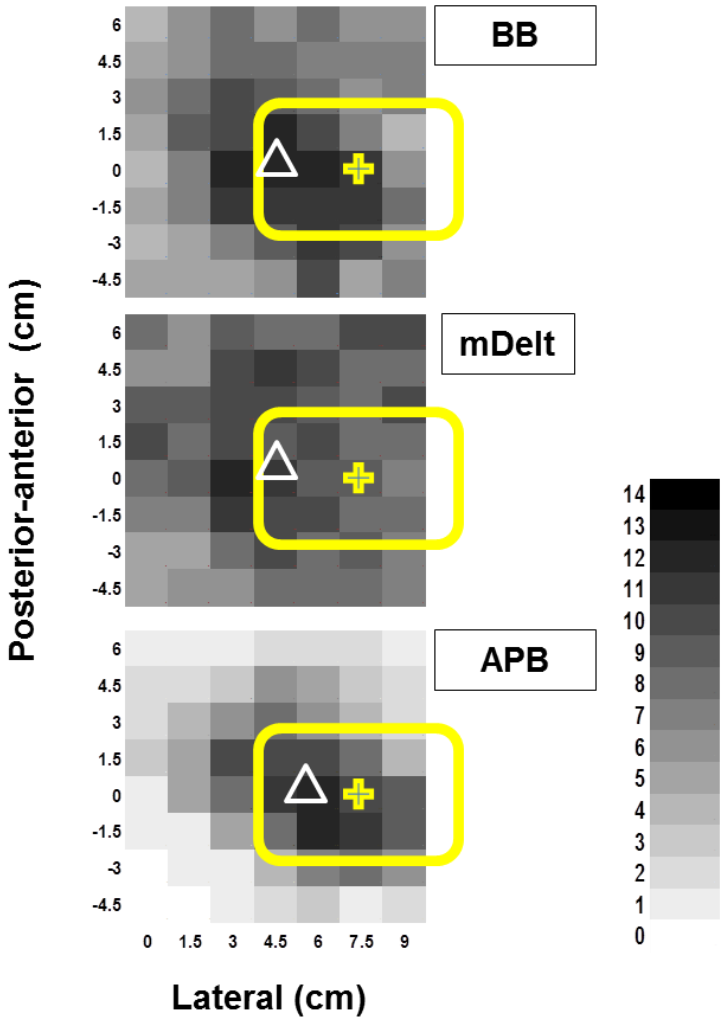


Figure 2.19: Mapped suprathreshold MEP responses and centroids in relation to the area of an arbitrarily-placed 7x5cm tDCS electrode pad.

Right (non-dominant) hemisphere cortical excitability maps with arbitrary tDCS pad electrode area overlaid on each. Composite maps were constructed on the basis of mean MEP responses evoked from the right hemisphere during mapping at each grid site. Shading at each pixel represents proportion of the 14 volunteer sample exhibiting a mean suprathreshold response at that pixel. White pixel=0 count. Black pixel=suprathreshold response elicited from all 14 volunteers. Yellow rectangle: placement and alignment of 7x5cm tDCS pad centred on C4. Filled cross: pad centre and mean site of C4 measured from study sample - coordinates x=7.55cm, y=0. Unfilled triangle: centroid of representation CoGs. Threshold calculated for each individual representation as = MIN + (0.05*(MAX-MIN) where MAX and MIN were respectively maximum and minimum mean evoked amplitudes at each individual muscle cortical representation.

2.12.2 Common preparation, TMS data acquisition and EMG recording apparatus

Participants were seated comfortably in an upright chair, with a table to the front upon which an LED biofeedback unit was placed (Figure 2.20). The non-dominant arm was supported in a manipulandum with the shoulder in 20° abduction, neutral flexion/extension and 20° internal rotation; elbow flexed to 90°; wrist in neutral in all planes and the hand relaxed.

As a standard during the current project, for high fidelity detection of surface EMG (De Luca, 1997)grounded bipolar surface electrode(Kendall Soft-E H59P) arrangements were placed longitudinally across the central region of the muscle belly of target muscles as required by the relevant protocol (Figure 2.21). An earth electrode was applied to the ipsilateral ulnar styloid. For mDelt the interelectrode distance was standardised at 10mm. For detection of EMG from the small APB muscle an interelectrode distance of 5mm was applied. These distances have been shown to reduce muscle crosstalk interference for surface electromyography (De Luca *et al.*, 2012).

Flying leads were connected from the surface skin electrodes to the amplifier, with wires roped to counter electromagnetic cross-interference. The EMG biofeedback unit was calibrated to full-scale deflection at 100% maximum voluntary contraction (MVC), as a subsequent guide to target levels of EMG activity at the relevant upper limb muscle of interest. The position of the vertex of the head was marked with a water-soluble pen according to the International 10-20 System (Herwig, Satrapi and Schonfeldt-Lecuona, 2003), with further markings made throughout the studies as required to indicate relevant loci of excitability.

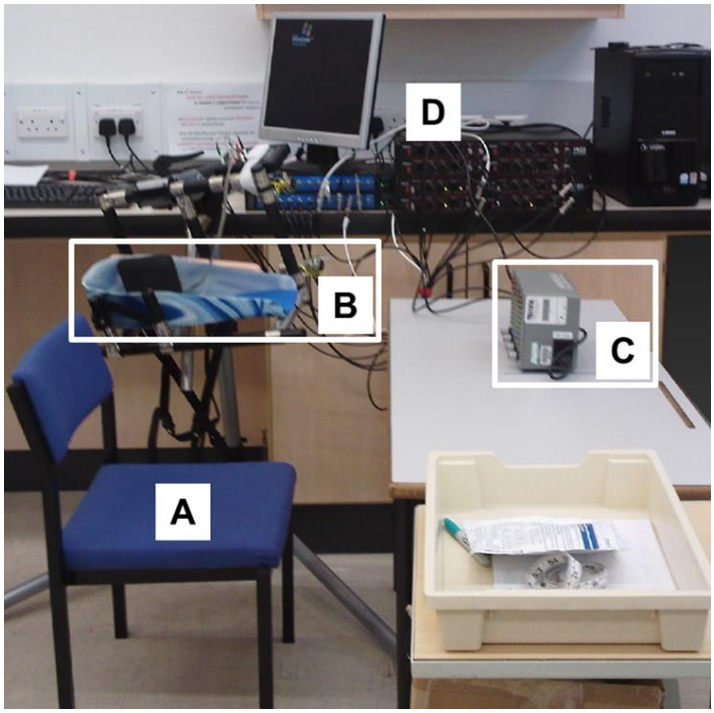


Figure 2.20: TMS measurement apparatus for definitive Study 3.

The participant was seated in an upright chair (A). The non-dominant arm was supported in a custom manipulandum device, which was fixed at elbow height (B). A biofeedback unit was placed on a table to the front. D: Amplification, storage and monitoring equipment.

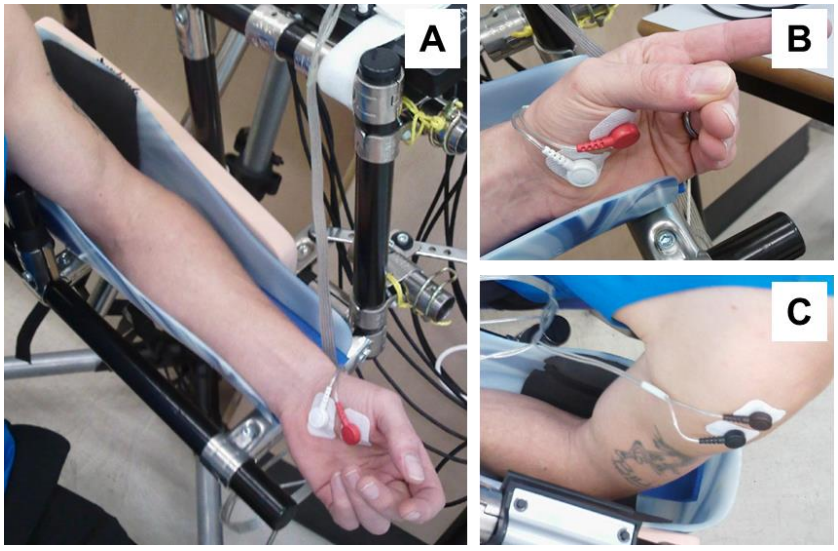


Figure 2.21: Non-dominant upper limb standardised positioning and electrode sites.

A: At rest, shoulder abducted to 20° and elbow flexed to 90°, wrist relaxed; bipolar electrode configuration over muscle belly of APB. B: Isometric contraction of APB; opposition of pad of thumb against medial aspect distal interphalangeal joint (IPJ) of middle finger, with all IPJs fully extended. C: bipolar electrode position on muscle belly of medial deltoid. During isometric muscle contraction, the lateral epicondyle of the humerus was stabilised laterally to prevent abduction, against a foam pad in the support tray.

Neurophysiological outcome measures were evoked by single-pulse or twin-pulse TMS specific to the relevant protocol, applied via two Magstim 200^2 monophasic magnetic stimulation generators (Figure 2.22), max output 2.2T (Magstim Co., Spring Gardens, Whitland, Carmarthenshire, SA34 0HR, UK)linked by a Bistim module (Magstim Co., UK). For TMS-evoked measurement during the definitive Study 3, where stimulation of specific loci was not required, a high power 90mm single circular coil (Art. 9784-00, Magstim Co., UK) was used. The benefit of using a circular coil in TMS studies is that, because the area of cortex stimulated is large, the coil can be consistently placed over the easily identified Cz central point (Shimizu *et al.*, 1999).

Although the stimulation intensities required to evoke a given output parameter are marginally greater, the reliability of the measures are equal to those evoked using a twin coil (Badawy *et al.*, 2011). Simplification of the data gathering protocol by using the single coil option substantially reduced the duration of measurement intervals in the definitive study. Because the single coil is not focal, it is also insensitive to use-dependent topographical focality changes (Nudo *et al.*, 1996) which can occur with changes in corticomotor excitability (Ziemann *et al.*, 2001) in the later consolidation stage of skill learning (Kleim *et al.*, 2004). Topographical shifting away from a pre-established scalp position could compromise the findings of studies investigating the interaction motor practise and tDCS intervention modalities (Thirugnanasambandam *et al.*, 2011).

The evoked electromyogram (EMG) from target muscles was amplified x1000 and bandpass filtered 1-2000Hz (Cambridge Electronic Design (CED) 1902, Cambridge Electronic Design, Cambridge CB4 0FE, UK), digitised at 4KHz (CED Micro1402) all controlled via Signal v4.08 software (CED) before storage on computer hard drive. The Signal software was also used to control the output of the Magstim stimulator unit. Background EMG was monitored on-line via PC monitor and off-line for evidence of inappropriate muscle activation when a resting state was required during data acquisition.

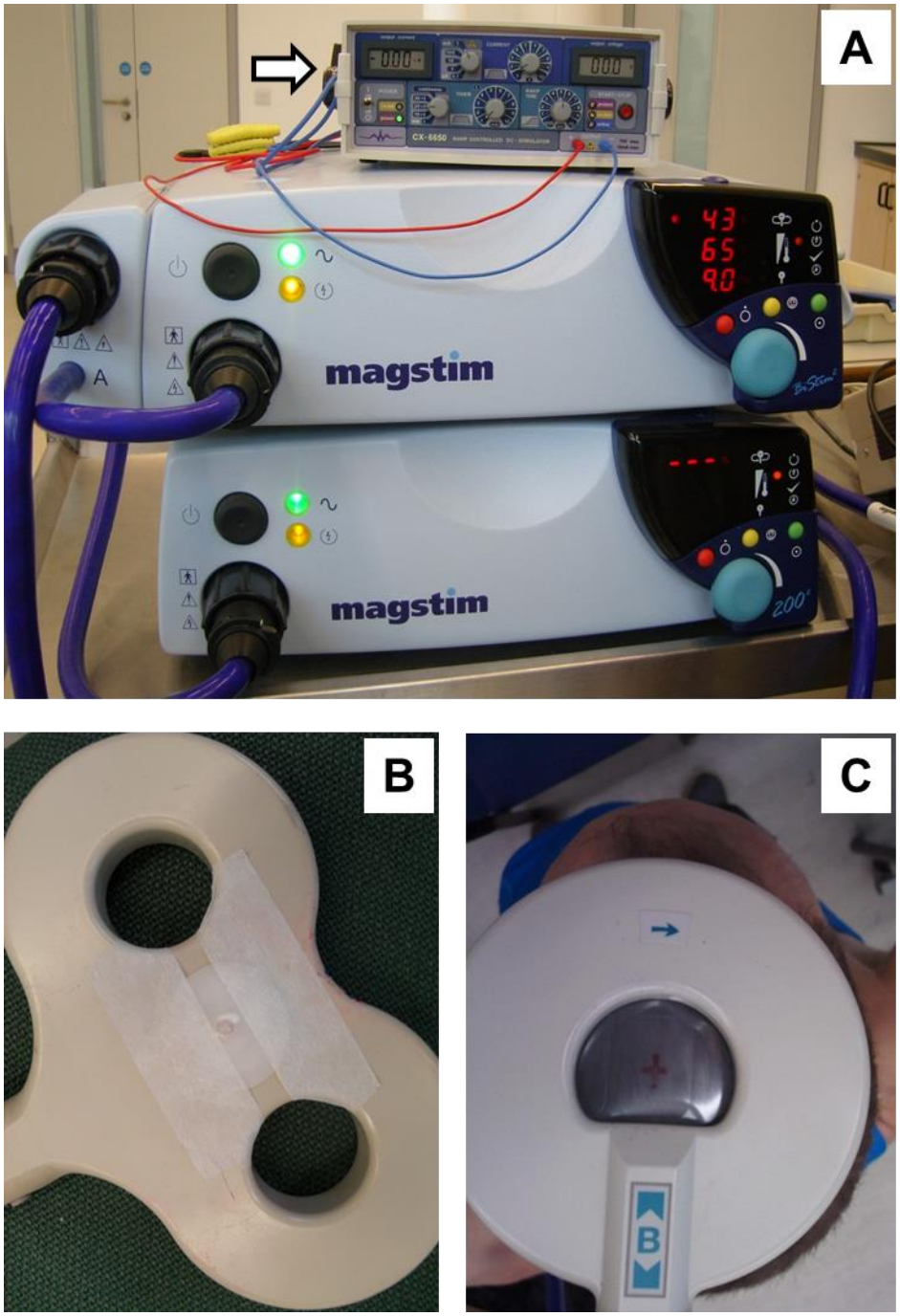


Figure 2.22: Stimulator componentry.

A: Blue units, Magstim 200^2 monophasic magnetic stimulator, (Magstim Co., UK); small box unit at top of picture (white arrow): tDCS stimulator (CX-6650, Rolf Schneider Electronic). B: Magstim flat, focal double 70mm coil used in background TMS study (Section VII.2.12.1) shown fitted with a grid locator disc as used for cortical mapping activity. C: Magstim high power 90mm single circular coil used in Study 3, located in position over Cz, positioned as illustrated with anticlockwise cortical current induction (opposite to clockwise arrow direction) for preferential activation of the non-dominant M1.

2.12.3 Determination of resting motor thresholds (RMT) of target muscles

Stimulus intensity was manually reduced until responses absent, and then incrementally increased again until RMT was determined as the stimulator intensity at which at least 5 of 10 MEPs were above a defined level of 50µV peak-peak (Figure 2.23) amplitude (Wilson, Thickbroom and Mastaglia, 1995).

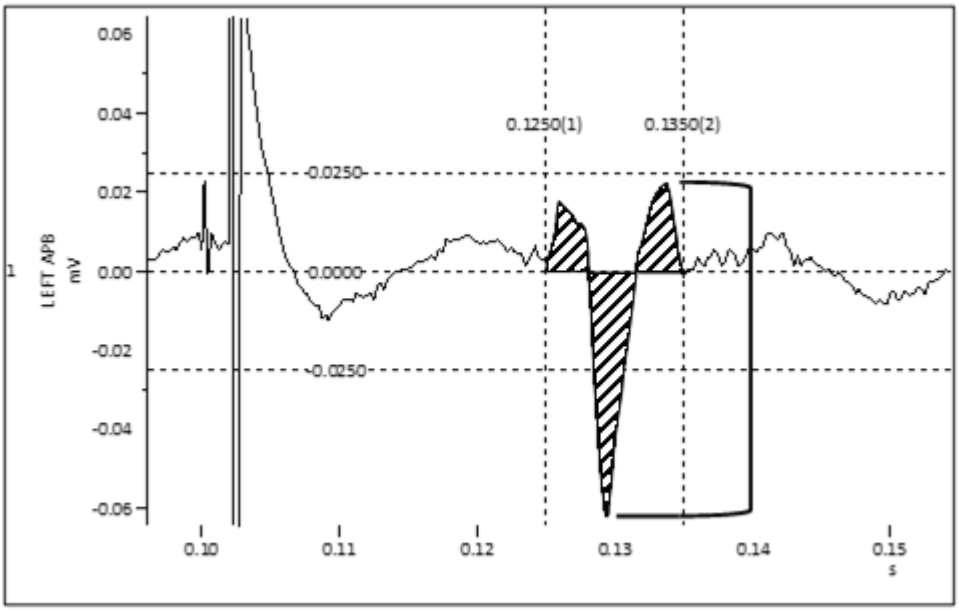


Figure 2.23: Measured parameters of MEP responses to TMS stimulus.

For illustration of several phenomena and measured parameters, a screenshot sample is presented of a single conditioned MEP response to a twin-pulse stimulus from a single subject. Motor evoked potential (MEP) response (waveform between vertical cursors) toa twin-pulse TMS stimulus (conditioning stimulus artefact at t=0.100s, test stimulus artefact onset at t= 0.102s), measured from resting-state APB. Abscissa: sampling time (seconds (s)). Ordinate: response voltage (mV). RMT was determined as the lowest TMS stimulus at which maximum peak-to-peak amplitude exceeded 50µV (vertical distance between horizontal cursors). For MEP amplitude (MTs, cortical mapping) the peak-to-peak amplitude (bracket) was gathered, while for MEP area responses gathered during recruitment curve protocols, the hatched area under the waveform between vertical cursors was measured.

2.12.4 Determination of active motor thresholds (AMT)

The site of maximum activation was checked while the participant maintained EMG activity at 20% of maximum. Stimulator output was reduced then increased in 2% increments until active motor threshold (AMT) was determined as an MEP response just visually discernible above background EMG activity at 20% MVCin 5 out of 10 responses (Devanne *et al.*, 2006; Wilson, Thickbroom and Mastaglia, 1995).

2.12.5 TMS stimulus-response curve and SICI procedures

Stimulus-response properties of the corticospinal system in humans depend on the interactions that take place along the corticospinal pathway. TMS-evoked stimulus-response curves(SRc) are considered to be the most sensitive method to detect changes in excitability, expansion and functional connectivity of corticomotor networks related to learning processes involving target muscles (Boroojerdi *et al.*, 2001a; Devanne *et al.*, 2002; Devanne, Lavoie and Capaday, 1997). TMS-evoked SRcs are thought to be reliable means of characterising corticomotor excitability over sampling intervals spaced over hours (Devanne, Lavoie and Capaday, 1997) and days (Carroll, Riek and Carson, 2001; Malcolm *et al.*, 2006)

The motor threshold for each relevant muscle and activity state obtained from the above motor threshold procedures were each used to calculate relative stimulus intensity scales, which were then manually entered as variables into a scripted Signal software programmes for random generation of stimuli at preset intervals.

During selective voluntary isometric activity of APB the participant maintained opposition between the pad of the thumb and the radial aspect of the distal interphalangeal joint (IPJ) of the middle finger, with the IPJs of all involved digits maintained in extension. In preparatory trials this pattern of opposition was found to preferentially activate APB. mDelt was voluntarily activated isometrically within the manipulandum for Study 3.

During the definitive Study 3, data was acquired in response to single-pulse TMS stimuli at 90, 100, 110, 120, 130, 140 and 150% of RMT/AMT (Davey *et al.*, 1999).Five stimuli were applied at each intensity level in randomised order, with interstimulus interval 5±10% seconds (van Kuijk *et al.*, 2009). During acquision of resting state curve data, as a sub-protocol for gathering of measurements of SICI, a further 5 single-pulse stimuli were applied in random order at 120% of RMT (SICI test pulse intensity control reference)with 10 twin-pulse repetitions, 80%/120% of RMT with 2ms interstimulus intensity. The respective conditioning (80% RMT) and test

stimulus (120% RMT) values for all measurement intervals was set relative to the baseline RMT value after the recommendation of Garry et al. . During acquisition of facilitated recruitment curves, muscle activity was voluntarily modulated by the participant to a target of 20% MVC indicated at the visual biofeedback unit.

We did not attempt to gather SICI responses from proximal muscles as the methods for gathering SICI from these muscles in the active state are not well-established as reliable. Our findings in respect of the high thresholds of proximal muscles in the background TMS study raised questions over the ability to reliably apply suprathreshold test pulses.

Prior to analysis of the stimulus-response curves (SRc) for each muscle and state, the MEP area responses from each stimulus state (Figure 2.23) were averaged as an arithmetic mean. MEP area was a preferred measure as the response from the entire topographical area of the cortex was accounted for. It is also thought that as a measure, MEP area is less sensitive to phase cancellation effects upon the output signal, which are caused by rapid firing of motor units as TMS stimulus intensity and facilitation activity increases (Kiers *et al.*, 1995).

2.13 Risks and precautionary measures associated with measurement and intervention techniques

2.13.1 Incidence of adverse effects

There were no incidences of adverse effects arising during the studies within this project.

2.13.2 TMS in measurement protocols

Safety concerns from heating, magnetic field exposure and induced voltages have been considered in recent publications, and the following precautions were taken during recruitment and as part of operational procedure during study sessions. The exclusion of individuals with skull plates, brain implants or who have had surgery to the head is thought to control adequately for heating effects (Rossi *et al.*, 2009). Rules requiring participants to remove jewellery from the head and neck, which might otherwise interact with magnetic fields constitutes good TMS laboratory practise and was applied routinely. No wires or electrodes were connected to the head or neck during TMS. To minimise the risk from the hazard of voltage induction, persons with implants to the head (Shimojima *et al.*, 2010) or thorax (Schrader *et al.*, 2005) were excluded from the study for the same reason. At no time did the total number of stimuli to be applied during a single session exceed 400, with an interstimulus

interval during continuous application not less than 5 seconds ± 10%. These parameters are well within the guidelines for TMS protocols (Rossi *et al.*, 2009).

2.13.3 Anodal tDCS

The aim of the study was to investigate the effect of non-invasive stimulation parameters which have been established to be safe (Webster, Celnik and Cohen, 2006). The Schneider CX-6650 constant current DC stimulator used in the study is a commercially available, custom-built device to a standard specification. It is marked as a prototype for scientific research only and is not certified for therapeutic treatment in humans, but has been used widely in tDCS research for the durations and at the intensities applied in the present study e.g. (Jeffery *et al.*, 2007; Power *et al.*, 2006; Fregni *et al.*, 2005b).

The intervention itself is experimental and which carries a minor risk of sensory irritation (Poreisz *et al.*, 2007) but without any history of physical harm other than understood and avoidable risks. To whit, minor local skin burns (Frank *et al.*, 2010; Palm *et al.*, 2008) associated with suboptimal application of electrical conduction interfaces. However, tDCS techniques have been shown to be safe and painless in controlled studies including healthy and neurologically-impaired participants when used in accordance with good practise guidelines (Brunoni *et al.*, 2011; Nitsche *et al.*, 2008). The maximum intensity and duration of the active group dosage used in the present project was ramped, current controlled 1.5mA for maximum 20 minutes continuously, using 7x5cm application pads, 1%w/v saline solution conductive medium, current density 43μA/cm^2, which are well within the guidelines for safety (Nitsche *et al.*, 2008; Hummel and Cohen, 2006; Bikson, Datta and Elwassif, 2009).Because there was no precedent for the application of anodal tDCS over consecutive days in the incomplete SCI population during study planning, a lower standardised current intensity of 1.0mA anodal tDCS was applied to participants during the pilot study 2.

2.14 Data summarisation

In order to support investigation and analysis of the data in the research studies, the following methods for summarisation of the data were utilised as detailed.

The data was analysed as absolute scores on interval scales, or converted to normalised data on ratio scales as indicated in the text.

Summarisation of raw data was carried out in four different ways to serve the aims of the particular analysis as indicated in the text:

2.14.1.1 Block summary

For a standard summarisation of multiple scores over a sampling period, such as task completion time or TPR scores, the arithmetic mean would be taken as a suitable method for summarising data which is not significantly skewed.

For example, for experience-dependent and between-conditions analysis of Task completion time, aggregate error or TPR, the sampled individual trial scores for the parameter of interest were summarised by taking the arithmetic mean. This mean score for each participant was taken as a summary.

2.14.1.2 Ranked trial summary

This novel approach was adopted in Study 1 to investigate the distribution of the 20-trial TPR datasets based on the central tendencies of the skill measure, independent of time. For investigation of sample mean TPR data distributions for each block of trials, the absolute trial TPR score for each participant was ranked from lowest (1) to highest value (20) as a group sample for each block. The data-points in each ranking for each volunteer in the sample were then summarised as an arithmetic mean TPR value for each ranking.

2.14.1.3 Trial-by-trial summary

This was a novel approach created to subserve investigation of the systematic association, or *co-regulation*, between the measured skill parameters completion time and error rate, over successive trials in a sampling interval. The raw data values for each parameter were separately summarised by taking the arithmetic mean across each 18-strong (Study 1) or 12-strong (Study 3) group sample for each consecutive successive trial. Using this approach, it was reasoned, random (asynchronous, zero mean) effects across the sample would be self-cancelling to reveal the combined effect of systematic (synchronous, non-zero mean) associations between the skill parameters over each 20- or 30-trial sampling interval, which would therefore be largely time-dependent (Burge, Ernst and Banks, 2008).

2.14.1.4 Error distribution summary

The absolute number of errors counted from at each rail angle was expressed as a proportion of the sum of error across all angles, for each participant and each 20-trial (Study 1) or 30-trial

(Study 3) interval. This provided for analysis of the interaction between target angle and spatial accuracy under different behavioural conditions. In the accuracy condition, a single participant produced a completely error-free set of 20 trials. In this situation, with the reasoning that spatial variability could not be shown to be less than the threshold error condition, the capacity for spatial error was assumed to tend to 1 at all targets and the distribution to be equal and recorded as 20% at each target.

2.15 Statistical methods

All statistical analyses were quantitative and carried out using computerised analysis software (SPSS version 15, SPSS Inc, Chicago, Illinois). Levels of significance were set at 5% for the rejection of null hypotheses. Details of the parametric and non-parametric statistical procedures utilised in each study may be found in the appropriate chapters. Here is presented a brief review of the techniques applied.

For all analyses the level of significance was set at 5% unless otherwise indicated in the text.

Because the present project was primarily concerned with investigation of the interaction of the between-subjects factor of intervention group and within-subjects factor(s) under repeated-measures study designs, mixed-model repeated measures analysis of variance (rmANOVA) statistical analyses were applied in general (Field, 2005). For the additional analysis of a co-variant factor on the outcome measures in Study 2, a mixed-model rmANCOVA was applied. Assumptions of both types of test were tested as discussed within the particular studies. A priori contrasts, post-hoc t-tests or paired comparisons were applied where indicated in the text. Details of corrections for multiple comparisons and tests of statistical assumptions are also given where necessary. Where indicated, the test of normality used was the one-sample Kolmogorov-Smirnov test for normality, because this statistic does not rely on parameter means and variances for the population to be valid(Field, 2005).

Non-parametric methods were applied to the analysis of the common subjective questionnaire, developed for use in the interventional studies 3 and 4 (the questionnaire is presented, Appendix E), because the distributions of group scores could not be guaranteed. For between-groups analysis of each 6-level ordinal scoring of perception numerical rating scales (NRS) categories, and the 5-level ordinal scoring of individual opinions in relation to group allocation, the Mann-Whitney U Test was applied(Hicks, 2005).

Where between-groups effect sizes are quoted, these are calculated in one of two ways. In order to provide for an estimate of the effect of the factor (r^2) on the variability of the model, Pearson's r was calculated from the t values at specific intervals (Equation 2.15-1)where the number of degrees of freedom = sample size n-2 (Field, 2005).The r values 0.1, 0.3 and 0.5 indicate small, moderate and large effect sizes respectively (Cohen, 1992).

$$\boldsymbol{r} = \sqrt{\left(\frac{\boldsymbol{t^2}}{(\boldsymbol{t^2}) + \boldsymbol{df}}\right)}$$

Equation 2.15-1: Calculation of effect size *r*at specific time intervals(Field, 2005).

Power analyses were applied where indicated in the text, to estimate the sample size required to reject a null hypothesis, with a given probability of a type II error (β) at 20% and therefore statistical power to reject the null hypothesis (1-β) at 80%and level of significance (α) at 5% in all cases. The sample size required was taken from tables (Cohen, 1992) or from the equivalent calculation for unpaired samples from parametric data, calculated from the effect size *d* (Equation 2.15-2).

$n = \frac{15.7}{d^2} + 1$, where $d = \frac{prevailing\ difference\ between\ independent\ means\ (\delta)}{mean\ standard\ deviation\ (\sigma)}$

Equation 2.15-2: Calculation of sample size *n* per group from the effect size *d* (Lerman, 1996).

The value 15.7 represents a generalisation of the formula when statistical power is at 80% and level of significance is at 5%

In all cases the standard deviations of independent samples were different and the hybrid root mean square (RMS) value *σ'* of the two sample standard deviations $\sigma 1$ and $\sigma 2$ was applied to calculate *d*, using the expression given at Equation 2.15-3.

$$\sigma' = \sqrt{\frac{(\sigma 1)^2 + (\sigma 2)^2}{2}}$$

Equation 2.15-3: Expression for root mean square standard deviation from differing standard deviations of independent samples (Lerman, 1996).

When calculating sample sizes from paired data, in order to take account of the increased statistical power associated with paired measures the value of *d* calculated from Equation 2.15-3 was further multiplied by a factor of $\sqrt{2}$ (Lerman, 1996).

In Studies 1, 3 and 4 measures of the correlation between variables are used. Parametric methods were applied using Pearson's Product Moment Correlation Coefficient (PMCC) where

the aim was to establish linear associations between variables. Where the nature of the association appeared to be non-linear, Spearman's Rho was applied with further investigations by regression curve analysis using the least-squares method (SPSS v15).

As a technique developed in Study 1 for investigation of the co-regulation between independent skill parameters of task completion time and spatial error score across a sampling interval, parametric associations were calculated between the trial-by-trial summarised datasets using PMCC. This procedure was carried out to test the null hypothesis that the strength of association between paired or independent correlations was not significantly different and therefore the same. Following r to z transformation as a procedure for normalisation of the Pearson's r sample distributions (Fisher, 1921) (Equation 2.15-4), comparison of differences in correlation across paired conditions were made in Study 1, using the series of computations indicated at Equation 2.15-5 (Meng, Rosenthal and Rubin, 1992). Comparisons of the differences between independent conditions were made with z tests at key sample points in Study 3, following Fisher's r-to-z transformation. The r value was transformed as Equation 2.15-4, followed by calculation of the test statistic applying Equation 2.15-6. The significance of the 2-tailed z tests were established from tables.

$$r' = 0.5 log_e \frac{[1+r]}{[1-r]}$$

Equation 2.15-4: Transformation of Pearsons r (Fisher, 1921).

$$z_{paired} = (r'_1 - r'_2)\sqrt{\frac{n-3}{2(1-r_x)h}}, \text{where } h = \frac{1-f\overline{r^2}}{1-\overline{r^2}} \text{ and } f = \frac{1-r_x}{2(1-\overline{r^2})}$$

r_x = correlation between predictors e.g. time; $\overline{r^2} = \frac{{r_1}^2 + {r_2}^2}{2}$

Equation 2.15-5: Computations for the test statistic for comparison of coefficients of paired samples (Meng, Rosenthal and Rubin, 1992).

$$z_{independent} = \frac{r'_1 - r'_2}{\sqrt{\frac{1}{n_1-3} + \frac{1}{n_2-3}}}$$

Equation 2.15-6: Computation for the test statistic for comparison of the correlation coefficients of independent samples (Fisher, 1921).

In Study 2, a single participant in the SHAM group failed to attend the second practise session. Thus, 2 values of a total possible 56 were missing from JTHFT and TPR datasets. Missing Value Analysis applying the estimation-maximisation (EM) method in SPSS was used to generate

missing outcome measure values following normalisation but prior to comparative analysis. EM estimation allows estimates to be adjusted using the available information, in order to find the maximum likelihood parameters of a statistical model (Schafer and Olsen, 1998). Estimation was made using sham group datapoints from all 7 measurement intervals, with assumption of dataset normality. The procedure was carried out over 25 iterations. Unit imputation of these values to the primary JTHFT and TPR datasets was automated as a program option prior to further analyses.

VIII. Research studies

Submissions and publications

- Study 1 has been submitted and accepted for publication in the Journal of Motor Behaviour.
- A poster summarising findings from Study 2 was presented at the 5th International Conference on Non-invasive Brain Stimulation 2013 in Leipzig, Germany on 19–21 March 2013
- A poster summarising the preliminary findings of Study 3 was presented at Physiology 2012, the annual meeting of the Physiology Society, at the Edinburgh International Conference Centre, UK on 2-5th July 2012.

Chapter 3. Study 1. Validation of a novel spatial motor skill learning task

3.1 Introduction

The ability to learn and retain manual skills is fundamental to the achievement of physical goals in everyday life, from elite sporting endeavour (Yarrow, Brown and Krakauer, 2009; Nielsen and Cohen, 2008) to the rehabilitation from injury where, in rehabilitation terms the practical benefit of task-dependent skill in an activity of daily living (ADL) may determine whether that behaviour persists and is adopted into the functional repertoire (Bruce H, 2004; Birkenmeier, Prager and Lang, 2010).

Internal environmental parameters are thought to be informed by active, error-based learning and external environmental states by more passive, use-dependent learning mechanisms (Diedrichsen *et al.*, 2010). Indeed, critical to the performance of even the most elite athletes is the interaction between the motivational goal (the difficulty of the spatial target and the rate at which the movement must be executed) and the capacity to manage the variability of the end-point (Yarrow, Brown and Krakauer, 2009). The M1 area of the brain is thought to be key to the encoding of these spatial end-points, which are subject to dynamic, experience-dependent processes of refinement and maintenance (Stark, Drori and Abeles, 2009; Graziano, Taylor and Moore, 2002).

A number of objective measures of motor skill are available to assess the level of upper limb manual dexterity or motor skill on continuous scales at the International Classification of Function and Disability (ICF) level of Activity, and have been co-opted as motor skill constructs. Most of these are derived from techniques for assessment of patient or employee dexterity (Yancosek and Howell, 2009). Tests can suffer from floor effects through an intolerance of spatial error in the outcome measure, or ceiling effects where the dependent variable (completion time) is no longer sensitive to the independent variable of interest, which in most cases is the time duration of a standardised sequential task. Furthermore, though it has long been recognised that spatial accuracy of movement is an essential parameter of skilled manual performance (Elliott, Chua and Helsen, 2001), there is as yet no universally-accepted definition for, or objective means of capturing spatial-temporal performance within a univariate

measure. In summary, the weaknesses present in current validated tests compromise objective evaluation of manual motor skill states or practise-dependent learning.

3.1.1 Towards a univariate measure of motor skill

The lack of a working definition for motor skill that provides for the outcome-driven measurement of real-world tasks is a barrier both for clinical and laboratory-based study designs (Shmuelof, Krakauer and Mazzoni, 2012).We began by defined practical motor skill in the following terms: *the ability to achieve a practical goal with spatial success over a limited quantity of time*(VII.1.11).It follows that, if participants are to be assessed on these criteria, the appropriate measurement system must detect and record the spatial and temporal domains with precision. To address this problem, we look to the motor control literature for inspiration.

In relation to human performance, Fitts and Radford considered the effect of movement rate on spatial variability with respect to a reaching target with the upper limb (Fitts, 1954). In practical terms, for a standardised target of difficult I_D (unit of measure, bits) a subject must on average successfully commit sensorimotor control resources matching or exceeding I_D to achieve reliable target accuracy in an aiming task. When repeated attempts at a sequence of *n* standardised targets are made over a mean movement time *t* the parameter of performance index I_P emerges as a *mean rate* of information transfer, with unit of measure bits/second (Fitts, 1954). Fitts described the function of the index of difficulty I_D of a single standard target (Equation 1.8-2) and, Introducing the expression for the temporal dimension, the minimum rate of information carrying capacity required to reliably achieve the spatial target, or performance index I_P could be defined (Equation 1.8-3).This parameter forms the basis for a quantification of the definition of skill.

More recent experimental observations back up Fitts' findings that, in a healthy human population sample the I_P in a simple reciprocation task is not significantly disturbed as a function of the trade-off between movement rate and spatial accuracy, leading to the conclusions that I_P represents a ceiling of human performance which is, within limits, insensitive to variations in movement rate (MacKenzie and Isokoski, 2008) or emphasis (Guiard, Olafsdottir and Perrault, 2011). Certainly, this appears to be the case for peak performances across a range of movement conditions, though it may be that varying behavioural/cognitive approaches or strategic preferences to a task might affect the constancy of this value (Guiard, Olafsdottir and Perrault, 2011).

A number of studies report aspects of the same phenomenon: I_P(Fitts, 1954), throughput (MacKenzie and Isokoski, 2008) and the quantity 'q' (Guiard and Olafsdottir, 2011), measured in bits/second, which in relation to a standardised target and the current outcome-based definition of motor skill equates to an accuracy rate. Taken together, this literature supports the principle of constancy of information transfer capacity I_P as an indicator of the sensorimotor resources at the command of the individual, including those affected by neurological injury, when applied via a standardised target or standardised sequence of *n* targets (Guiard and Olafsdottir, 2011). Thus, given fixed environmental conditions, the theory suggests that there might be a common solution to the speed/accuracy trade-off function of tasks which is relatively constant, independent of internally, or externally-driven behavioural approaches to the task.

The classic Fitts' law task involves series of discrete or, alternatively reciprocating movements between points (Huys *et al.*, 2010). Let us further consider a task comprised of a closely spaced array of *n* near-identical standardised targets, of similar reaching distance and dimensions, where a volunteer is asked to carry out a sequence of reciprocating movements between a start point and the targets in succession. Then, from Equation 1.8-3, because the targets are standardised and the kinematics of each movement sequence are similar, I_D might be approximated as a constant, U, with successful targeting expressed as scores on the target in the reciprocating sequential task and ΣU is the sum of successful scores (Equation 3.1-1).

$$I_P = \frac{1}{t} * \Sigma U$$

Equation 3.1-1: Expression for IP in relation to a sequence of similar targets.

Where I_P quantifies the information carrying capacity or, as we have defined it, the skill level demonstrated over a single task trial in achieving a proportion (*n*- spatial errors) of the targets over a period of time, unit of measure scores/second. But let us invert the expression for the conveniences of working with number that is in most cases will be greater than 1, and also because $1/I_P$ reflects the construct of efficiency in a standardised task. That is, an increase in efficiency is associated with a reduction in the consumption of information-carrying resources to achieve task success. The expression also concurs with the concept of motor skill being semantically aligned with the direction of task achievement (or task productivity) in completion time, the dominant metric in clinical measurement of skill. We applied the term Task Productivity Rate as a descriptive term of the parameter $1/I_P$ (Equation 3.1-2).

$$TPR = t/\sum(n - errors)$$

Equation 3.1-2: Task Productivity Rate (TPR) skill measure, unit of measure seconds/score.

Within a productivity-centred interpretation of the Fitts' paradigm the scalar TPR measure considers the *minimum* utilisation of information resources to the completion of a task activity, and therefore is only sensitive to activity with a successful outcome on the target. Likewise, within our constrained workspace information-transfer only has meaning in terms of the outcome. In the interests of providing unequivocal feedback of spatial performance to both participant and investigator, we specify a binary spatial outcome for each target in the standardised task – accuracy or error, as a targeting attempt will conclude with the object of the idealised practical task (e.g. a peg) resting within the margins of the effective target area, or not. This approach concurs with the classic Fitts' task paradigm which calls for a constrained repetitive task where activity only has meaning in terms of proximity to a target centre (Fitts, 1954).

3.1.2 Definition of Task Productivity Rate as a skill measure

We applied Task Productivity Rate (TPR) as a scalar, interval measure of motor skill in the current project. The TPR score, defined as above (Section VII.1.12) was taken as *the mean time taken to score a successful placement on a set of discrete spatial targets and return to the start position in a standardised task*. The unit of measure applied was *seconds per score* (s/score).

3.1.3 Development of a skill task to deliver the TPR outcome measure skill parameters

The design issues relating to implementation of arrays of identical targets in relation to a sequential task are discussed (VII.2.9.1.1). Briefly, as a strategy for improving the linearity of the measurement scale and to facilitate motor learning, I_D was manipulated across the target array to create a scale of target difficulty. Instead of manipulating the physical form of the target, we introduced variation in the complexity of grasp manipulation demands by implementing a non-repeating rail motor sequence, applied across an adjustable target sequence in a closely spaced array. Randomisation was applied to the order of target angle orientation to control for possible order and positioning effects, which are known to affect movement times (Pratt, Adam and Fischer, 2007). To minimise a possible interference with declarative sequence learning (Ghilardi *et al.*, 2009) this was designed to be attempted in

consecutive order from left to right in all cases. This approach also provides for multiple solutions to the target matching problem (Wong and Whishaw, 2004; Hoffmann *et al.*, 2006), in accordance with the theory of motor abundance (Latash, 2012).

3.2 Research questions

3.2.1 Research question 1

We sought to answer the primary research question in relation to the importance of behavioural bias upon skilled motor output: does the TPR univariate measure of motor skill vary significantly dependent upon behavioural variation? Upholding the null hypothesis would not conclusively prove that this measure was stable across *all* conditions, but it would provide evidence upholding the null hypothesis that the TPR skill measure does not vary significantly due to changes in behavioural approach alone. This would support our notion that, within the limitations of the study design there might exist a common solution to the speed/accuracy trade-off which provides a stable metric of spatial motor skill.

3.2.2 Research question 2

Fitts' law holds for static levels of skill (Guiard, Olafsdottir, & Perrault, 2011; MacKenzie & Isokoski, 2008) but ongoing task practise is thought to result from a breakthrough in the trade-off between speed and accuracy (Shmuelof et al., 2012; Reis et al., 2009). In the current study design this would be interpreted from a significant improvement in the TPR score. We tested the sensitivity of the TPR measure as an indicator of motor learning, with the null hypothesis that the skill measure did not significantly change during free practise.

3.2.3 Research question 3

It was theorised that target difficulty, and hence both the sensorimotor resources required to achieve target matching could be manipulated by varying the orientation of the rail target. We sought to establish whether target difficulty constituted a stable scale for observations of spatial error, hence providing a reliable feedback condition for modulation of movement rate. The null hypothesis was that, based upon observations of error, the relative target difficulty did not vary significantly during *free practise* conditions.

3.2.4 Research question 4

The skill parameters of motor output and sensory experience are intimately associated in optimisation of goal-centric motor performance through adaption (van Beers, 2009) which informs the development of more sophisticated motor engrams (Novick & Vaadia, 2011). As a parsimonious means of considering the relationship between the skill parameters we observed and analysed the linear associations between the proxy skill parameters of MRST completion time and error rate during each condition. The null hypothesis was applied, that *manipulation of behaviour* would not give rise to a significant difference in the strength of linear association between the skill parameters under the speed- or accuracy-emphasis conditions compared to the normative state.

3.3 Methodology

Prospective within-subjects, cross-sectional quantitative study.

3.4 Methods and materials

3.4.1 Recruitment

Eighteen healthy, right-handed (modified Edinburgh Handedness Inventory; median 100, range 67-100) adult staff or student members of the University population (10 females, 8 males; age: median 29, range 22-67) who were free from history of neurological deficit, upper limb orthopaedic condition or uncorrected visual impairment provided written consent to participate in this study, which was approved by the Research Ethics Committee of the School of Health Sciences and Social Care, Brunel University, London. Each volunteer carried out the study protocol during a single interval lasting around one hour, at a behavioural laboratory facility. All activities were designed and carried out in accordance with the Declaration of Helsinki. No financial or other inducement to take part in this study was provided.

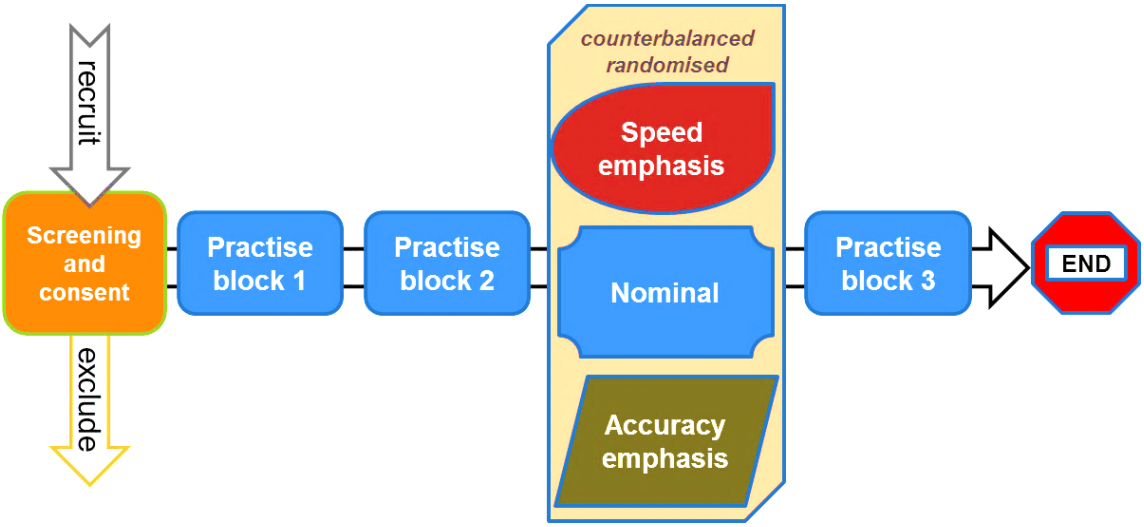


Figure 3.1: Study design schematic.

The mean completion time of 2 blocks of 20 MSRT trials provided the metronome tempo guiding the completion rate of the subsequent movement-rate guided blocks. Behavioural manipulation is applied in 3 blocks, which are presented in counterbalanced randomised order: each block emphasises completion speed, task accuracy or nominal (combined speed and accuracy) conditions. Subjects were allowed 4-6 practise trials before each practise block and condition. A final block of trials at self-selected speed were gathered in order to assess short-term learning effects.

3.4.2 Motor Skill Rehabilitation Task study design, task apparatus and administration

Based upon the findings of the literature review, a novel motor task was developed in a process summarised in Section VII.2.9.1. Briefly, through an iterative process of prototyping and outcome evaluation with the assistance of both healthy and tetraplegic volunteers, a peg and rail task design was formulated in order to fulfil design criteria, ensuring that the TPR outcome derived from task performance could be applied to target groups with a wide spectrum of grasping abilities. The task apparatus and administration of the MSRT, sampling of task completion time and error count and derivation of the TPR outcome measure under the different practise conditions were as presented in General Methods (VII.2.9.4).

3.4.3 Study protocol

The basic unit in this protocol was the 'block' which comprised of 20 consecutive MSRT trials. All task activities were carried out with the left upper limb only, to investigate the formation of dextrous activity from a consistent naïve state across the right-handed volunteers. All participants followed an identical protocol (Figure 3.1) each participant was assigned a 5-element randomly generated non-repeating motor sequence code. From this code, the rotational angles of the MSRT rail components were set, to 0, 30, 60, 90 or 120 degrees with respect to the centre-line of the apparatus. Speed-emphasis, accuracy-emphasis and normative behavioural blocks were also carried out in order according to a counterbalanced randomisation chart, with each of the 6 possible sequences therefore being carried out by 3 participants.

3.4.3.1 Instructions and applied motivation

Standardised guidance observed by the researcher, and instructions to participants were as presented in Appendix B. Further specific instructions in relation to behavioural conditions were issued as indicated below.

3.4.3.2 Practise blocks

Participants were asked to carry out the task as accurately and quickly as possible using any preferred grasp pattern or approach, using the left arm only. This statement was repeated once at the start and twice during the course of every block of 20 MSRT trials, with the terms 'quickly' and 'accurately' spoken in alternating order, in order to prevent biasing of behavioural approach to the task practise. Firstly, after explaining the procedure, participants

were directed to carry out practise 4-6 trials of the MSRT to demonstrate understanding of the instructions. Immediately following this, each participant carried out 2 blocks of 20 practise trials, in blocks 1 and 2. The mean completion time from these 40 calibration trials was immediately summarised from the spreadsheet record and used to calculate the movement rates for normative, speed- and accuracy-emphasis blocks using the method outlined in

Table 3.1.

Participants then carried out a total of 60 behavioural manipulation trials, with the behaviour manipulated by guidance of movement rate as discussed below. Following these, participants carried out a final free practise block of 20 trials under the same conditions at practise blocks 1 and 2 in order to evaluate the sensitivity of the outcome measure to motor learning over the duration of the protocol.

3.4.3.3 Behavioural manipulation– effect of movement rate upon spatial accuracy

After the approach of MacKenzie et al. (2008), we manipulated the movement rate as the independent variable, as this is a quantitative parameter for which it is simple to provide guiding feedback to participants. As described below, we used a metronome to impose a movement rate which would reliably guide participants to complete MSRT trials at a rate of our choosing.

In order to analyse the consequence of changing approaches to a task upon spatial accuracy, we applied a completion time 10% shorter than the calibration speed during speed-emphasis trials, 10% longer during accuracy emphasis trials and also at the normative (guide) speed. In order to entrain manual performance, after the method of Reis et al. (2009) participants were instructed to attend to the sound of an aural metronome tempo (Aroma Scroll-Wheel AM-703 Aroma Music Co., Ltd., Bao'an District, Shenzhen City, Guangdong, P.R.China, www.aromamusic.cn.) as a guide to movement rate (Reis *et al.*, 2009) and use the metronome as a guide to movement between each of the 12 critical positions involved in a single full trial of the MSRT task.

Table 3.1: Calculation of metronome guide rates for behavioural conditions.

Because the MSRT comprises of 11 idealised movement intervals between 12 spatial point positions in a full trial, 11 metronome beats signal the start of successive movements with each trial ending on the 12th beat. BPM: beats per minute/metronome cadence. The calibration movement rates are derived from the mean MSRT completion time calculated from 40 trials over practise blocks 1 and 2.

Behavioural emphasis	Target completion time relative to measured calibration time (*G*)	Movement rate calculation (60*11)/*xG*	Example solution (assuming calibration time of 5.00 secs), BPM
Normative	1	(60*11)/*G*	132
Speed	0.9	(60*11)/*0.9G*	147
Accuracy	1.1	(60*11)/*1.1G*	120

After entraining the movement rate to the metronome beat and demonstrating this by carrying out 4-6 trial blocks, participants completed a block of 20 trials at each metronome-guided movement rate in counter-balanced, randomised order (

Table 3.1). Task completion times were monitored on-line and volunteers advised to adjust movement rate accordingly if this diverged from the target. In all behavioural conditions participants were asked to maintain the best accuracy possible while moving at the indicated cadence. Completion times were monitored on-line throughout and, if necessary, participants verbally guided to attend to the required movement rate.

3.5 Analysis

3.5.1 Data summarisation methods

The data was analysed as absolute scores on interval scales, or converted to normalised data on ratio scales as indicated in the text.

Data in respect of completion time, error rates and TPR was **ranked trial, block, trial-by-trial or error-distribution** summarised to facilitate analysis of various data parameters. See Section VII.2.14 for an explanation of these 4 techniques.

3.5.2 Statistical tests

The data was analysed as absolute scores on interval scales, or as normalised data on ratio scales as indicated in the text.

Research questions 1 and 2 were tested by one way repeated measures Analysis of Variance (rmANOVA) with the main factor of practise/behavioural emphasis BLOCK to control for the possibility of rejecting a null hypothesis. Tests were applied to assess the effect of task practise on error rate, completion time and the TPR skill measure relative to the normative/baseline state. The factor of BLOCK (3 levels) was applied in each case.

Approaching research question 3, separate analyses on the error distribution-summarised datasets across free practise and behaviourally manipulated blocks was made by two-way rmANOVA, with main within-subjects factors BLOCK (3 levels) and ANGLE (5 levels) in each case. The same analysis was applied to investigate variations in error distribution observed under behavioural manipulation. For further analysis of the differences in error distribution between paired behavioural conditions rmANOVAs were carried out with BLOCK (2 levels) and ANGLE (5 levels). Mauchley's test of sphericity was applied to all analyses and, where significant, degrees of freedom were adjusted using the Greenhouse Geisser Epsilon correction. Bonferroni corrections were applied for paired and post hoc comparisons of main effects as indicated in the text.

For research question 4, parametric associations between the error trial-by-trial summarised skill parameter datasets were calculated between the trial-by-trial summarised datasets using Pearson's Product Moment Correlation Coefficient (PMCC) to test the null hypothesis that the strength of association between paired correlations was not significantly different. Following this, comparisons of differences in correlation across paired conditions were made using the Steiger's Test method advocated by Meng, Rosenthal, & Rubin (1992), following r-to-z transformation (Fisher, 1921). The 2-tailed significance of the Z values was established from tables (Field, 2005). r_x (dependency between the predictor variable (time) series') were calculated as the PMCC r between the time series for the relevant behavioural conditions. A Bonferroni correction was applied for multiple comparisons such that the level of significance was 2.5%.

All statistical tests were performed using SPSS (v15, SPSS for Windows, Rel 15.0.1.2007, Chicago: SPSS Inc).

3.6 Characterisation of TPR datasets and method of establishing central tendency

3.6.1 Characteristics of data distributions

The residual accuracy/completion time plot distribution of a single subject shown in Figure 3.2was typical of those produced by all subjects, both in practise and guided-rate blocks. This subject achieved full accuracy in 13 of the 20 trials. Those trials with lower residual accuracies occurred to the left of the plot and were associated with faster completion times. The data points were loosely clustered around a central tendency of residual accuracy n=4 and completion time of approximately 7s.

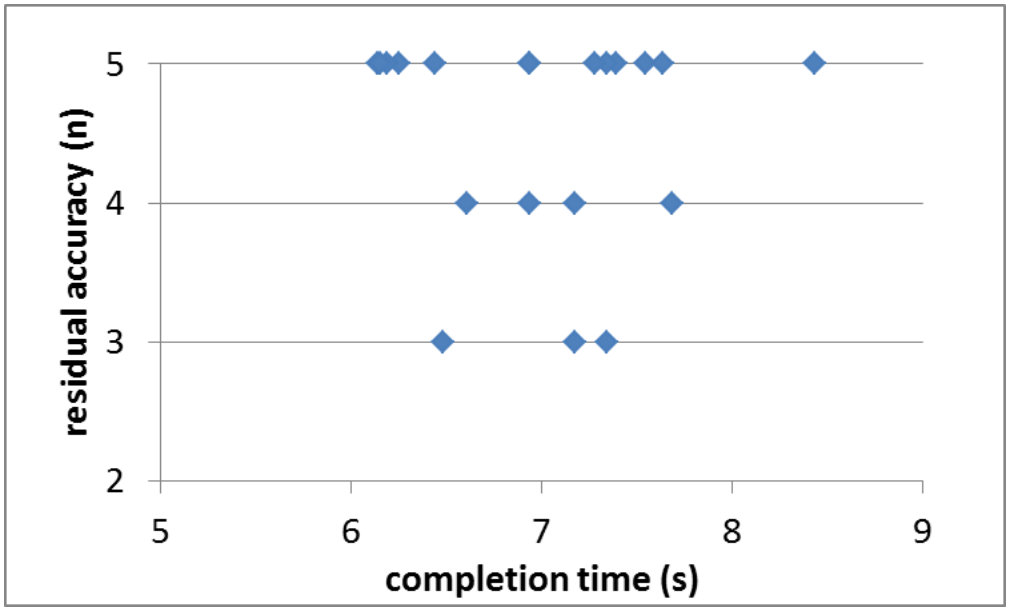


Figure 3.2: Plot of residual accuracy versus completion time in MSRT practise from a single subject.

Each datapoint represents the result of a single trial. The plot is characterised by a clustered central tendency for completion time at around 7.2s and residual accuracy of approximately 4.5. From participant 15, free practise block 2.

With TPR calculated from the skill parameter scores of each individual trial and plotted consecutively over time (Figure 3.3A), there appeared to be no systemic association between variation in TPR and the passage of time and trial-on-trial variation in performance appeared random within limits. The overall impression was of a statistical, rather than direct relationship between movement rate and accuracy which perhaps reflected a model of human motor control with an innate motor noise component (Burge, Ernst and Banks, 2008).

For the purposes of obtaining a central tendency, the sample was collapsed with respect to the abscissa value (time). With the same sample of 20 trial TPR scores placed in ranked order independent of time, a mildly curvilinear association could be seen where both the absolute value and the rate of change increase with rank order, suggestive of a mildly exponential, positively skewed distribution across the ordinate axis (Figure 3.3B). In general the distribution was smooth, with slightly more pronounced rank-on-rank increases in TPR score at approximately 1.3, 1.6 and 2.0 s/score. These could be interpreted as a signal of the I_D of individual targets predicted in our derivation of the outcome measure concept, where TPR increases markedly as the performance index I_P for a target of particular difficulty is exceeded. If so, this characteristic may be a signal that the strategy of manipulating target I_D to create an error scale, and thereby simulate real-world experience of tasks where a margin for error is explicit even at the elite level (Bartlett, Wheat and Robins, 2007), has the intended effect.

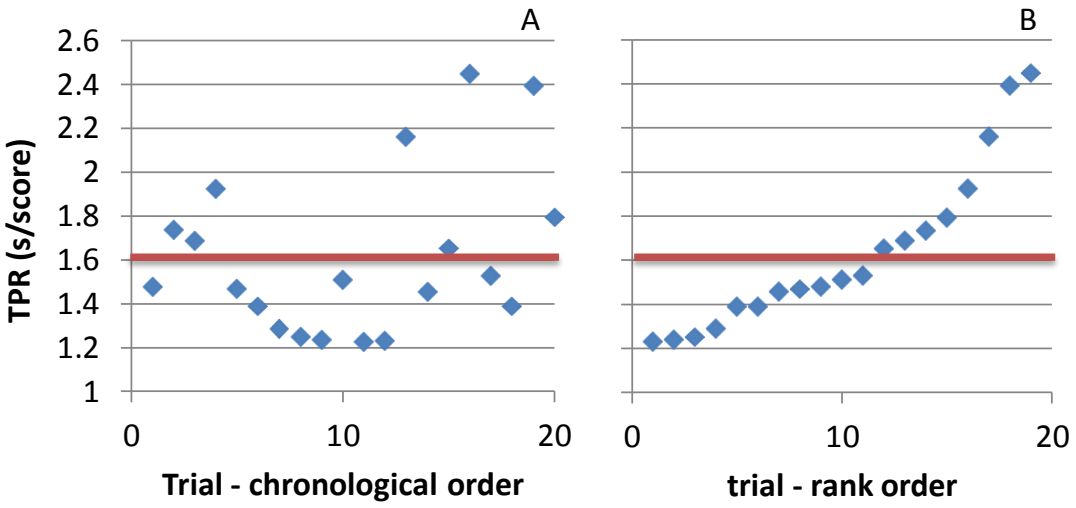


Figure 3.3: Typical distributions of Task Productivity Rate data from the single subject.

Task productivity rate (TPR) calculated for each individual trial, completion time/residual accuracy (s/score). A) consecutive chronological order B) rank order from the same, single subject. Superimposed red line: arithmetic mean TPR value for this distribution was 1.612 s/score. From participant 15, free practise block 2.

Expanding the scope of the characterisation to look at the general effect of task experience on skilled task activity across the group, visualisation of trial-by-trial summarised TPR data over successive trials (Table 3.4) revealed a noisy relationship between the two variables. However, in addition to the random component there appeared to be a common systematic trend effect to improvement i.e. reduction in TPR score which continued throughout the session (which totalled 120 recorded trials).

Analysing the linear dependency between the two variables by taking the descriptives and the PMCC (Table 3.2) practise block 1 represented early learning from the naïve state. This was characterised by a moderate strength of association which was significantly different to zero. The coefficient of determination, r^2, suggested that over 25% of the variability in the model was due to this relationship. As practise continued over the subsequent two practise blocks, the second and third of which were separated by 60 blocks of behaviourally-manipulated trials, the strength of the systematic component was reduced and did not reach significance. However, when the association between the variables was considered as a continuous learning experience over the three free practise blocks (assuming that practise under behavioural manipulation did not have an effect), this resulted in a model demonstrating a highly significant moderate strength of association between the variables which described over 30% of the variability between successive trials, or task experience (which might be considered the independent variable) and TPR score (the dependent variable).

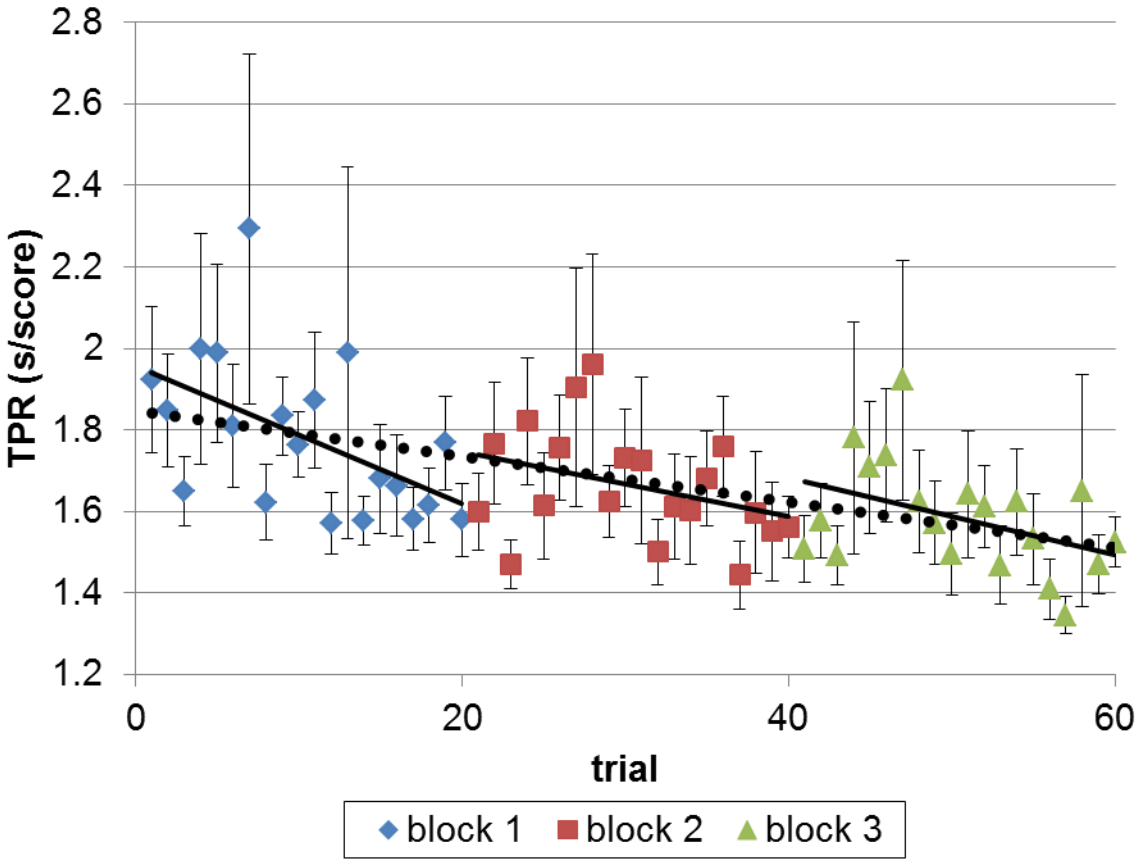


Figure 3.4: The effect of experience upon trial-by-trial sample mean TPR score over 3 successive free-practise blocks from the naïve state.

Trial-by-trial summarised data points ±SEM. Behavioural manipulation trials took place between free practise blocks 2 and 3.Solid black lines: separate linear association trend lines superimposed for each block of 20 trials. Dotted line: combined trend line for the linear association across all three practise blocks.

Table 3.2: Linear dependency between trial-by-trial summarised raw TPR score and task experience over 3 successive free practise blocks, and across session of 60 trials.

Descriptives (mean value; SEM, standard deviation (σ), PMCC (r) and significance (p) values summarising the strength and significance of linear association between trial-by-trial summarised mean TPR scores (s/score) and the factor of time (successive trial). r^2: coefficient of determination. Calculated separately for each block of n=20 trials, each trial summarised across the 18-strong sample. Separate comparison across n=60 datapoints. Linear association significantly different to 0, *p≤0.05; ***p≤0.001.

Practise block	*n*	*Mean (s/score)*	*SEM*	σ	*r value*	*p value*	r^2
1	20	1.781	0.043	0.191	-0.522	0.018*	0.272
2	20	1.664	0.031	0.138	-0.346	0.135	0.119
3	20	1.585	0.030	0.135	-0.414	0.070	0.171
Combined	60	n/a	n/a	n/a	-0.565	<0.001***	0.319

3.6.2 Distributions of Task Productivity Rate data

Prior to further analysis it was considered important to justify the use of the arithmetic mean as the measure of central tendency, we independently characterised the mean distributions and the normality for each ranked summarised data distribution of each of the 6 conditions. The outcome of this investigation influenced our selection of a suitable summary measure of central tendency. The positive skewing of the sample means data was consistent across all blocks, and none differed significantly from normality (Table 3.3). We concluded that the arithmetic mean was appropriate to be used as the preferred measure of central tendency to summarise individual TPR datasets for subsequent analysis.

Table 3.3: Descriptives and statistics for the TPR outcome under variation in practise conditions.

Mean ranked block data descriptives, distribution characteristics and normality statistics for the TPR outcome (s/score).SEM: Standard error of the mean. Skew: skewness. 1 K-S: 1-sample Kolmogorov-Smirnov test of normality, D statistic and p value. n=20 for all samples.

Trial block	Mean	SEM	Skew	1 K-S	
				D	p value
Practise Block 1	1.781	0.122	2.275	0.180	0.533
Practise Block 2	1.660	0.104	1.587	0.146	0.790
Speed emphasis	1.845	0.164	1.917	0.194	0.438
Accuracy emphasis	1.762	0.069	1.602	0.153	0.740
Norm emphasis	1.741	0.092	1.123	0.159	0.694
Practise Block 3	1.588	0.099	2.069	0.177	0.555

3.7 Results

3.7.1 The effect of manipulating behavioural approach on measured parameters

Results of one way rmANOVA are given at Table 3.4 and are portrayed graphically at Figure 3.5. Variation in mean movement rate had a highly significant effect upon task completion time in the accuracy-emphasis condition at 109.9±1.4% and speed-emphasis at 90.6±0.5% completion times respectively compared to the norm condition. Pairwise, there were highly significant differences ($p<0.001$) in completion time compared to the normative movement rate (95% CI accuracy .08 to .11; speed -.14 to -.06).

Table 3.4: The effect of free practise and behavioural manipulation on skill parameters and TPR.

The results of separate 1 way rmANOVAs for the effect of free practise, or manipulation of behavioural conditions, across 3 blocks of 20 MSRT trials. Significant at *p≤0.05, p≤0.01, ***p≤0.001.**

Behavioural condition	*Skill parameter/ measure*	*F value*	*df*	*P value*
Free practise	**Error**	**2.193**	**2,34**	**0.127**
	Time	**51.553**	**2,34**	**<0.001*** **
	TPR	**4.745**	**2,34**	**0.006****
Behavioural manipulation	**Error**	**6.291**	**1.055,17.943**	**0.021***
	Time	**144.960**	**1.184,20.133**	**<0.001****
	TPR	**2.465**	**1.387,25.009**	**0.121**

Compared to the normative state, when speed was emphasised to reduce the completion time by 10% the mean aggregate error approximately doubled to 200.6±50.6% of the norm value. In contrast, when we increased completion time thereby allowing for increased accuracy, error was reduced to 78.8±20.4% of that in the norm state. The main effect of varying movement rate upon the occurrence of error was significant, with pairwise comparisons indicating a significant difference between the speed and accuracy conditions, P=0.005, 95% CI 0.36 to 2.08. However, error during either of these conditions relative to the normative state was not significantly different.

Although varying movement rate away from the normative condition in either direction resulted in an increase in the TPR score (speed emphasis: 7.1±3.0%, accuracy emphasis: 2.3±2.3%) the main effect of behavioural manipulation on TPR was not significant.

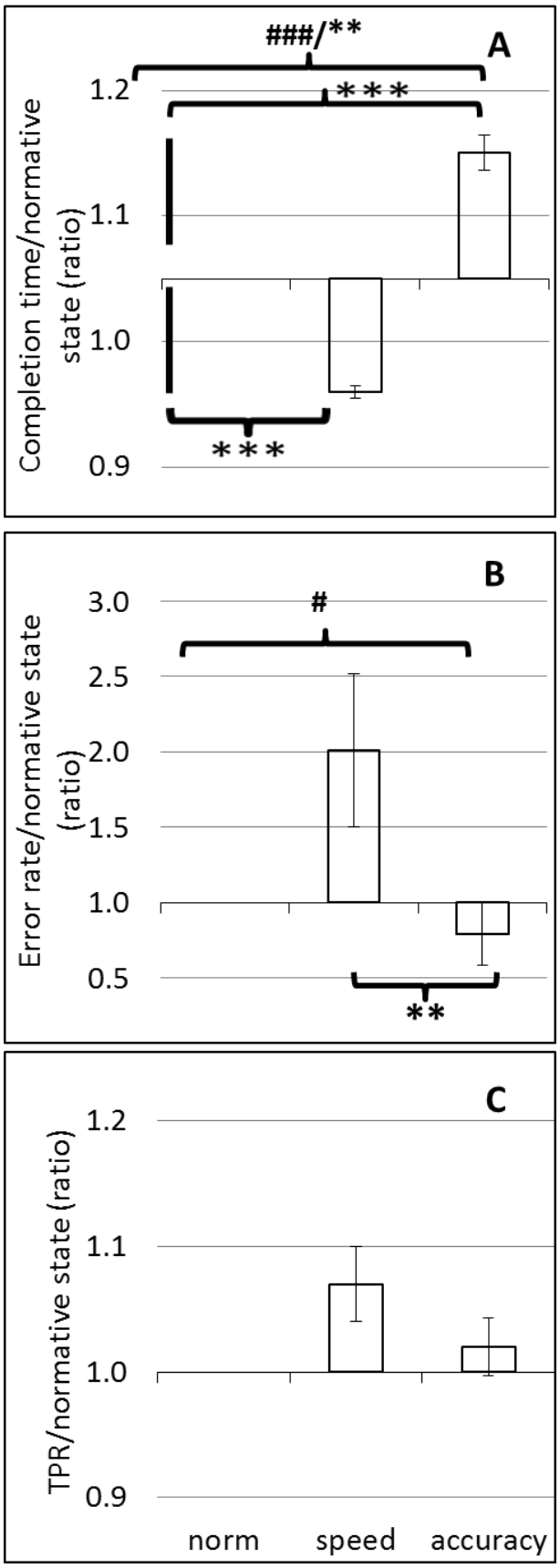


Figure 3.5: Effect of manipulating behavioural emphasis on the outcomes of MSRT performance relative to the norm condition.

A) Completion time: significant differences between and across all conditions.

B) Aggregate spatial error: significant main effect only.

C) TPR skill measure, stable across and between conditions.

Symbols: Main effects #P≤0.05 ##P≤0.01 ###P≤0.001; pairwise comparisons *P≤0.05 **P≤0.01 ***P≤0.001

Data collection over a single block of 20 trials under each condition.

3.7.2 The effect of free task practise on measured parameters

The main effect of practise on task completion time was highly significant (Table 3.4). Normalised mean completion times relative to baseline for block 2 were 5.0±1% reduced compared to baseline, and block 3 11.2±1.2% reduced compared to baseline (Figure 3.6). Contrasts showed that *successive* changes in completion time were highly unlikely to be due to chance ($p<0.001$) blocks 2-1 95% CI -.08 to -.02; blocks 3-2 95% CI -.10 to -.03; blocks 3-1 95% CI -.15 to -.09.

While, relative to the baseline condition, the error rate was increased slightly by 4.1±15.0% in the second block and by 31.5±13.1% in the final block the main effect of practise on targeting error was not significant.

The main effect of practise on the derived TPR skill measure was significant between the first and final free practise blocks with the pairwise change in the mean TPR score indicating a highly significant improvement in skill between practise blocks 1 and 3, $p=0.001$ 95% CI -.16 to -.04. However, pairwise contrasts showed the change in normalised score between *successive* blocks was not significant, with the block 2 mean score at 95.1±3.3% and final block 3 mean score at 89.9±2.2% of baseline TPR value.

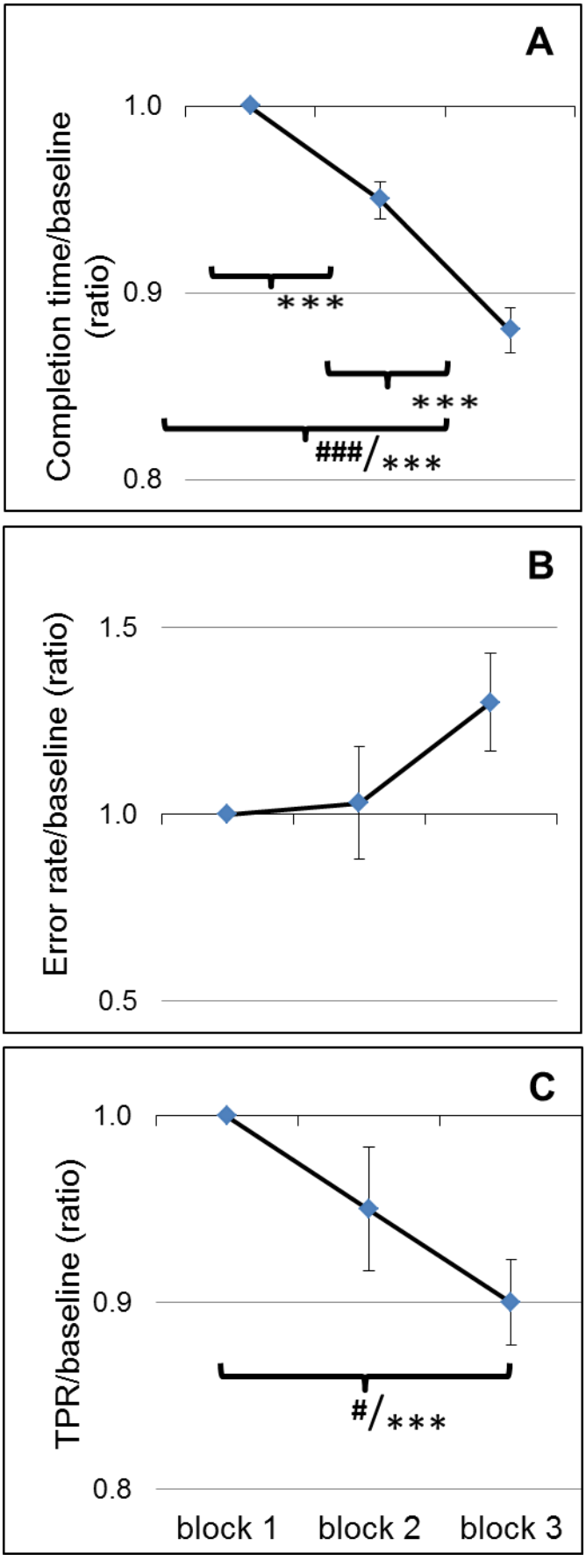


Figure 3.6: Effect of MSRT free practise on task outcomes over 3 successive blocks of 20 trials each.

Data normalised to relevant block 1 baseline score per participant.

Note that the behavioural guidance protocol was implemented between practise blocks 2 and 3.

A) Completion time: highly significant differences between and across all conditions.

B) Aggregate spatial error. No significant differences between or across conditions.

C) TPR skill measure: significant main effect of practise with highly significant difference shown between block 3 and baseline score only.

Symbols: Main effects #p≤0.05 ##p≤0.01 ###p≤0.001; paired comparisons with Bonferroni correction *p≤0.05 **p≤0.01 ***p≤0.001

3.7.3 Distribution of error by rail orientation angle

Observation of error distribution by target orientation showed that, in general peg placement at rail orientations of 30° and 60° were most reliably achieved while the highest spatial error occurred with placement attempts at rails oriented 120° and 0° from the apparatus midline (Figure 3.7 and Figure 3.8). Because error was expressed proportionally in these analyses, comparisons by the main effect of BLOCK were not relevant.

Separate 2-way rmANOVAs were carried out to establish the stability of apparent target difficulty in the datasets gathered, firstly under *free practise* conditions to address research question 3. Here, we found a highly significant effect of rail ANGLE (Table 3.5). Pairwise comparisons by ANGLE showed a significant difference in proportional error between targets oriented at 0° and 60° p=0.012 95% CI .02 to 0.16 (Fig 4). The interaction BLOCK*ANGLE was not significant, demonstrating that the there was no effect of practise experience on the distribution of errors across the array.

Table 3.5: Independent effect of free practise and behavioural manipulation conditions on error rate distribution across target orientations.

Separate 2-way rmANOVAs on effects of free practise and behavioural manipulation. In each analysis, main effect of rail ANGLE (5 levels) and interaction with BLOCK condition (3 levels) on the dependent variable proportional error rate across target orientations. Rail angle order was randomised per participant. Significant main effect/interaction at *p≤0.05 **p≤0.01 ***p≤0.001.

Comparison conditions	*Main effect/ interaction*	*F value*	*Df*	*P value*
Free practise	**Rail angle error**	**4.836**	**2.671,45.415**	**0.007****
	Block* angle error	**0.691**	**8,136**	**0.699**
Behavioural manipulation	**Rail angle error**	**10.475**	**2.505,42.588**	**<0.001*****
	Block* angle error	**2.571**	**4.142,70.407**	**0.043***

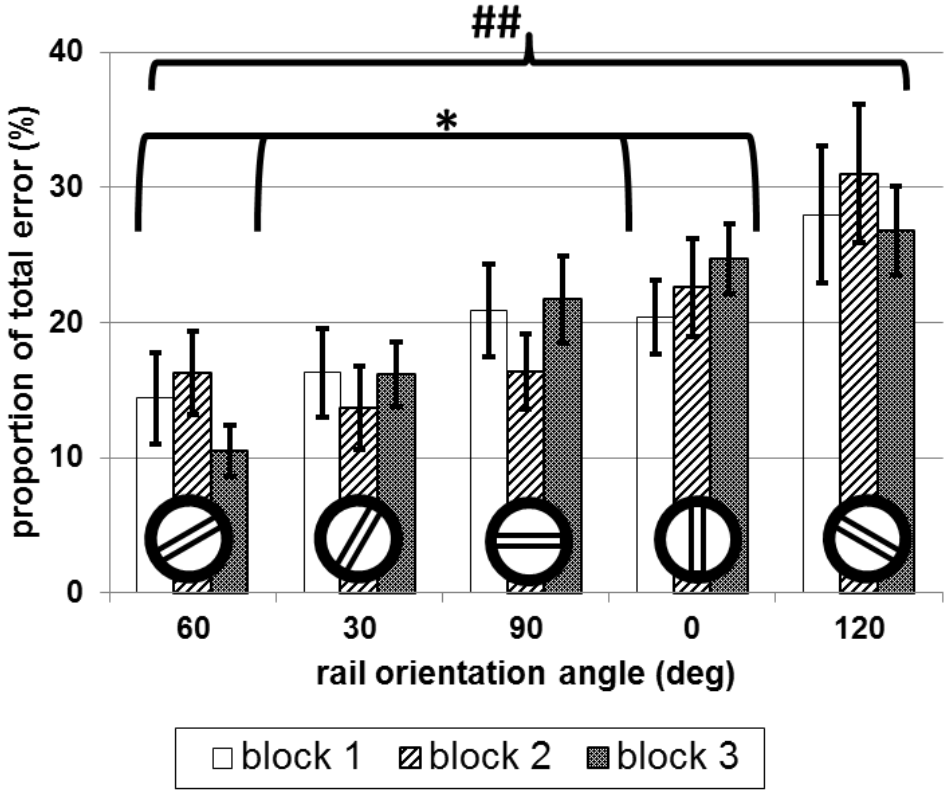


Figure 3.7: Proportional error distribution over successive blocks of free task practise.

Proportional scaling of observed error distribution did not vary significantly over successive practise intervals and was quasi-linear according to the angle of target rail orientation. . 2 way rmANOVA. Rail angle in increasing order of observed error, left to right. Distribution of error count per rail angle as a proportion of the total error count across all angles per interval ± SEM, over successive blocks. Angle graphic illustrates the respective rail orientation as seen by the participant. Significant main effect ##p≤0.01 , Significant paired contrast *p≤0.05.

2 way rmANOVA of the effect of *behavioural manipulation* on error distribution revealed a highly significant main effect of rail target ANGLE and also a significant interaction between behavioural BLOCK and ANGLE (Table 3.5). Pairwise comparisons of variations in error distribution between target orientations revealed significant pairwise differences $p \leq 0.05$ between target orientation 0° and targets at 30°, 60° and 90°; 30°, and between the 120° orientation and the 30° and 60° targets (Figure 3.8).

Further investigating the significant effects, three separate 2-way rmANOVAs were carried out for pairwise comparison of the differences in error distribution between specific guided states with Bonferroni correction at the level 1.67%. In all comparisons, the within-conditions effect of rail target ANGLE on the distribution of error was very highly significant. On the basis of the significant BLOCK*ANGLE interaction found between speed-emphasis and accuracy-emphasis conditions (Figure 3.7) paired t-testing was carried out within each rail orientation angle, with Bonferroni correction to 1%). Significant differences between conditions were identified only at the 0° target $t(17)=-2.932$ $p=0.009$ 95% CI -0.275 to -0.045, speed- vs. accuracy-emphasis (Figure 3.8).

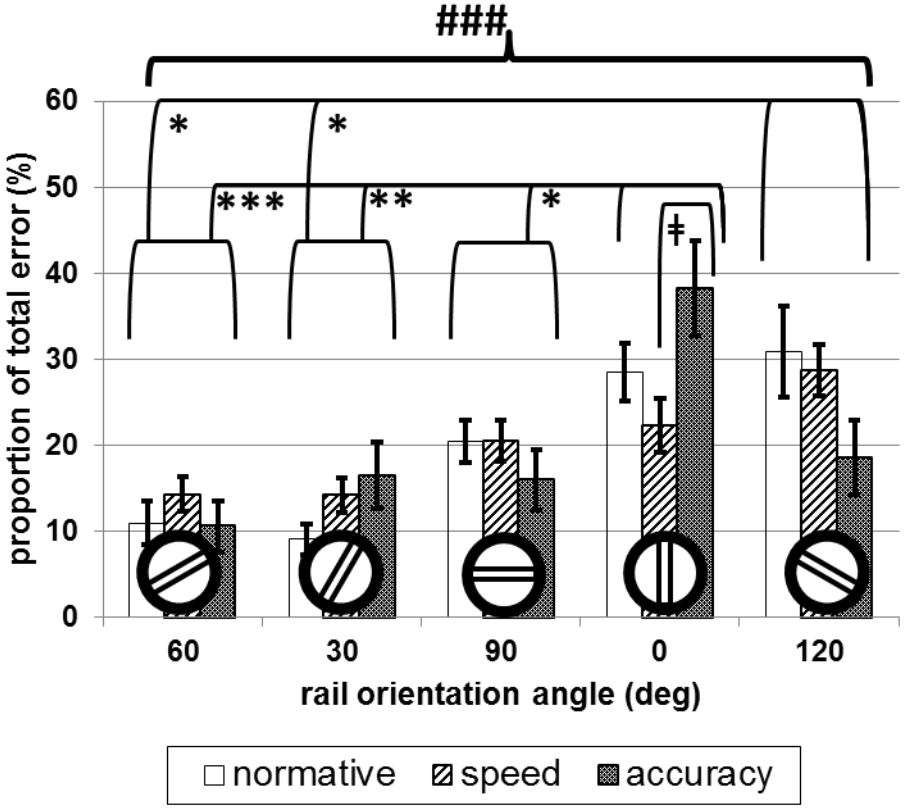


Figure 3.8: Highly significant variations in error distribution occur as a result of behavioural manipulation.

Behavioural manipulations: normative speed, speed-emphasis and accuracy-emphasis conditions. 2 way rmANOVA. Angle graphic illustrates the respective rail orientation as seen by the participant – ordered left to right as per Figure 3.7. Highly significant main effect ### $p<0.001$ of rail angle with pairwise comparisons across conditions *$p\leq0.05$ **$p\leq0.010$ ***$p\leq 0.001$. Significant pairwise comparison at 5 rail angles between speed- and accuracy-emphasis conditions, Bonferroni corrected ‡$p\leq0.01$.

Table 3.6: Separate 2 way rmANOVA comparisons of error distribution between paired manipulated behavioural conditions.

Repeated comparisons of the separate and interaction effects of rail ANGLE (5 levels) and practise BLOCK (2 levels) on error distribution across targets of varying orientation. Rail angle order was randomised per participant. Significant main effect/interaction at *p≤0.05 ***p≤0.001. Corrected level of significance for multiple rmANOVAs ǂ p≤0.0167

Comparison between behavioural conditions	Main effect/ interaction	F value	Df	P value
Normative-speed	Rail angle error	7.833	2.256,38.359	<0.001***
	Block* angle error	1.640	2.346,39.880	0.203
Normative-accuracy	Rail angle error	10.220	4,68	<0.001***
	Block* angle error	2.191	4,68	0.079
Speed-accuracy	Rail angle error	6.730	4,68	<0.001***
	Block* angle error	3.542	4,68	0.013*ǂ

3.7.4 Evidence for co-regulation behaviour between task completion time and error rate

The association between the trial-by-trial summarised skill parameters over each block condition was separately compared by PMCC with r and p values shown in Table 3.7.

No significant correlations between completion time and error rate were found to occur over any of the free practise blocks. Furthermore, associations between skill parameters under speed- and accuracy conditions were found to be non-significant. However, constraint of movement under the moderate, normative condition revealed a moderate strength positive association between the skill parameters which was significantly different to zero.

Table 3.7: Associations between sample mean trial-by-trial summarised task completion time and error score under respective block conditions.

PMCC r: Pearsons Product Moment Correlation Coefficient (PMCC). Skill parameters summarised as sample means over successive trials. Cognitive manipulation blocks took place following practise block 2 and prior to practise block 3. *Significant association between skill parameters p≤0.05

	Practise blocks				Behaviourally-guided blocks		
	1	2	3		speed	accuracy	norm
PMCC r	0.219	0.292	0.015		-0.250	0.015	0.455
p value	0.355	0.212	0.962		0.287	0.952	0.044*

Paired differences in correlation coefficient for behaviourally manipulated conditions relative to that found in the normative condition were compared using the Steiger's Test method advocated by Meng and colleagues (Meng, Rosenthal and Rubin, 1992), with the null hypothesis that the paired correlation coefficients were not significantly different to each other, and a 2-tailed alternate hypothesis. From Equation 2.15-4, the respective r values were transformed to r' scores:

r'_{speed} = -0.255; r'_{norm} = 0.491; r'_{acc}=0.015

r_x = linear dependence between the predictor variables i.e. r_x between speed and normative time series = 0.299; r_x between accuracy and normative time series = 0.245.

$\overline{r^2}sp\_norm = \frac{r_{speed}{}^2 + r_{norm}{}^2}{2} = \frac{0.063+0.207}{2}$=0.135; $\overline{r^2}acc\_norm = \frac{r_{acc}{}^2 + r_{norm}{}^2}{2} = \frac{0.0002+0.207}{2}$=0.207

Then $f_{sp\_norm} = \frac{1 - 0.299}{2(1-0.135)} = 0.405$, and $h_{sp\_norm} = \frac{1-((0.405)(0.135))}{1-0.135} = \frac{0.946}{0.865} = 1.094$;

and $f_{acc\_norm} = \frac{1 - 0.245}{2(1-0.207)} = 0.476$, and $h_{acc\_norm} = \frac{1-((0.476)(0.207))}{1-0.207} = \frac{0.901}{0.793} = 1.136$;

From Equation 2.15-5

$$z_{paired} = (r'_1 - r'_2)\sqrt{\frac{n-3}{2(1-r_x)h}}$$

Then for $z_{paired\ speed\_norm}$ = (-0.255 – 0.491)$\sqrt{\frac{15}{(2(1-0.299)1.094)}}$

= (-0.746)$\sqrt{\frac{15}{1.534}}$ = -2.333.

And for $z_{paired\ acc\_norm}$= (0.015-0.491)$\sqrt{\frac{15}{(2(1-0.245)1.136)}}$

= (-0.476)$\sqrt{\frac{15}{1.715}}$ = -1.407.

From tables (Field, 2005) these Z values equated to a two-tailed significance of p=0.020 for the paired difference in correlations between speed-emphasis and normative, and p=0.159 for the difference between accuracy-emphasis and normative conditions. With Bonferroni correction to level of significance 2.5%, the 2-tailed alternative hypothesis was accepted only for the comparison between speed-emphasis and normative completion time/error correlation coefficients.

3.8 Discussion

3.8.1 TPR did not vary significantly across behavioural conditions

Despite highly significant variations in guided movement rates the TPR skill measure did not vary significantly compared to the normative rate condition, upholding the null hypothesis. As variations in movement rate were imposed during behavioural guidance, there was a corresponding systematic impact on spatial accuracy such that TPR was not significantly affected. The results suggest that, when the variable of learning experience was controlled for, the sample of healthy subjects maintained a stable mean level of skill as we defined it, even when movement rates varied systematically by as much as 20%. The null hypothesis for research question 1 was upheld.

The generalizable inference is that, within limits, around an optimal peak performance specific to the individual and the task, there exists a common solution to the speed/accuracy trade-off function. This result is consistent with Fitts' Law (MacKenzie and Isokoski, 2008) but is, we believe, the first time that the theory has been applied in respect of a practical manual visuomotor activity involving complex movement sequences. Though the mean scores between behavioural conditions were not significantly different the data did show that reducing or increasing movement rate relative to the normative level resulted in a negative impact on TPR scores. The ability to demonstrate information carrying capacity of the individual may fall off away from an optimal central value which could be partially dictated by the spatial parameters of the target (Fitts, 1954) or, indeed the behavioural approach (Guiard, Olafsdottir and Perrault, 2011). However, the results concur with those found in analysis of performance levels in a simple reciprocation task, which likewise did not significantly differ over a range of movement rates (MacKenzie and Isokoski, 2008).

3.8.2 Skill improved significantly during motor practise

We additionally interrogated the data for evidence that the TPR skill measure was sensitive to practise and did, in fact, significantly vary over practise time as an indicator of motor learning. TPR responded significantly to MSRT practise, indicating that the improvement in motor skill seen was highly unlikely to be due to chance. As a straightforward quantitative finding consistent with other approaches to measurement of learning-dependent changes in the

speed-accuracy tradeoff (Reis et al., 2009), a *breakthrough* occurred such that the skill level significantly improved and the null hypothesis for research question 2 was rejected.

Even under the standardised instruction motivating subjects to prioritise the accuracy and speed of movements equally, highly significant reductions in *completion time* were found between successive practise blocks. But we found that the improvements in the TPR skill outcome were much less marked, and achieved significance relative to the naïve state only over an extended period of practise. Thus, though the increases in error rate over successive free practise blocks were not statistically significant, it was evident that variation in spatial end-point variability must have had an important effect and skill improved more conservatively than we might otherwise have assumed if considering task completion time as the skill outcome. This suggests that the speed-accuracy relationships observed during behavioural manipulation may operate to some extent during free practise of the task.

As a potential limitation which may undermine direct comparisons between free practise and externally-modulated behavioural conditions, there are thought to be differences in the coupling between changes in speed and accuracy depending upon the demands of the task. Under velocity constraint a linear relationship between speed and accuracy is thought to hold (Schmidt *et al.*, 1979) which may not be the case when accuracy and reaching distance alone are constrained and a logarithmic relationship might apply (Fitts, 1954). More fundamentally, these outcome relationships may be driven by differences in kinematic behaviour which emerge from the specific temporal and spatial constraints of the task (Bongers, Fernandez and Bootsma, 2009) and the particular behavioural motivation (Guiard, Olafsdottir, & Perrault, 2011). Despite these considerations, in comparing the datasets gathered during free practise against those gathered during the behaviourally-constrained, normative movement rate the mean of sample absolute TPR measures obtained from free practise blocks 1 and 2 (during calculation of the normative movement rate) differed by only 1.2% from the mean TPR score measured during the subsequently performed normative guided state. This is an impressive convergence of skilled behaviour in view of the possible statistical noise introduced by the complexity of the sequential targeting task and the external factor of auditory behavioural guidance.

It has been suggested that discontinuities in the speed-accuracy tradeoff (Sleimen-Malkoun *et al.*, 2012) and related changes in velocity-time plots during reaching (Huys, 2012; Huys *et al.*, 2010) may arise primarily due to the precision constraints of the task because they are seen in relation to targets of higher difficulties. Because the reaching amplitude and targeting

constraints of the current MSRT task were fixed within-subjects, these parameters probably interacted with net decreases in end-point reaching precision which arise with increasing movement rate (Meyer et al., 1988; Schmidt, Zelaznik, Hawkins, Frank, & Quinn Jr., 1979). Conversely, even given a generous reach time (as in the accuracy-emphasis condition) the mechanism of on-line correction can statistically never fully control for random motor errors which arise during the enactment of target approach and placement movements (Meyer et al., 1988) or imperfect systematic sensory estimates of the true end-effector and/or target positions (Shadmehr et al., 2010). But because the target scoring of the MSRT is dichotomous rather than continuous (for example, as a standard deviation relative to an ideal target centre) any behaviour-dependent differences in TPR score might be difficult to observe at low movement rates.

3.8.3 Spatial error as a modulating parameter in skilled motor activity

In the MSRT design paradigm target difficulty was manipulated, not by the conventional method of modifying component dimensions but by employing a reverse kinematic principle (McFarland *et al.*, 2008; Faraway, 2003) to enforce more or less complex grasp combinations across the motor sequence. The aims of this design criterion were two-fold: to provide for target difficulty scaling in a fashion designed both to improve the linearity of measurement, and to facilitate a naturalistic motor learning experience. The design also provided for control for order effects by implementing true randomisation of target orientation across the sample.

We found that the scale of target difficulty, as inferred from observations of error distribution did not vary significantly when analysed across free practise blocks and maintained a reliable distribution constituting a continuous quasi-linear scale. In relation to research question 3, the null hypothesis was upheld.

By varying the single parameter of target orientation, the difficulty of otherwise identical sub-task elements was modulated to increase the range and sensitivity of the aggregate error measure which we theorise provided for explicit feedback of spatial error to inform aspects of future performances, including movement rate. The finding that over successive practise sessions the error distribution did not significantly vary also lends support to the theory that skill learning reflects improvements in global control parameters such as refinement of reaching kinematics rather than improvements based upon the accuracy constraints of specific

targets (Shmuelof, Krakauer and Mazzoni, 2012). The behavioural advantage of varying movement rates based on recent feedback of targeting error may be that movement rates can be regulated over the short-term, around a level which achieves the task objective according to the behavioural emphasis under operation (Brenner and Smeets, 2011).

Significant variations in the distribution of error were detected between the extremes of speed- and accuracy emphasis behavioural conditions. It is thought motor learning results from reduction, not negation of net spatial variability (Muller and Sternad, 2009) with minimal correction of spatial error to optimally achieve the goal outcome (Todorov, 2004) while the variability of spatial trajectory in reaching increases as a function of movement planning both in relation to the accuracy demands of the task (Sleimen-Malkoun et al., 2012; Burge et al., 2008) and the intensity of muscle activations (Schmidt, Zelaznik, Hawkins, Frank, & Quinn Jr., 1979). It has been found that subjects' movement rate during a simple reciprocation task can be rapidly modulated by ongoing observations of accuracy during motor performance (Brenner & Smeets, 2011) and we also found that behavioural manipulation of mean movement rate during task execution had a significant and directly proportional effect upon overall error rate.

Taken together, our results suggest not only that movement rate during free practise of the MSRT could have been modulated partially by the effects of target difficulty upon the observation of error, but also that systematic variations in error at the most challenging targets were most evident to potentially inform the subsequent actions of subjects. Sensory observations of error are thought to interact with prior experience to modify ongoing motor performance (Novick and Vaadia, 2011). Thus, both the stability of the TPR outcome measure across behavioural conditions and the improvement in TPR scores over the duration of the session may reflect the operation of a simple mechanism for modulation of human behaviour in complex motor tasks, whereby subjects' movement rate may be a response to systematic changes in the distribution of errors across targets of varying difficulty, as well as the overall rate of targeting errors as task repetitions continue. The possibility that individuals may be sensitive to errors incurred at more challenging targeting elements in a complex task concurs with the recent finding that, in a simple cyclic reciprocation task accurate targeting is immediately followed by increased movement rate while targeting error has a slowing effect on subsequent movement (Brenner & Smeets, 2011). Thus, rather than basing future physical strategies upon an abstract knowledge of uncertainties which accrue in the human motor system, observations of spatial error may regulate completion time in an ongoing adaptation of the movement plan (Burge et al., 2008).

3.8.4 Systematic associations between the skill parameters

Our results in respect of the calculated TPR skill measure were consistent with Fitts' Law in showing that, despite modification of behavioural approach under parallel skill states the construct of motor skill based on information transfer (of which the TPR is a derivative) was statistically robust. We have suggested that the criterion governing movement rate in the MSRT task was observation of spatial error. But was there any direct evidence of co-regulation between the skill parameters and, furthermore was there evidence that behavioural manipulation significantly altered co-regulation behaviour?

A significant linear correlation between sample mean movement rate and spatial error scores, where error rate varied proportionally with completion time was only observed when behaviour was constrained at the normative movement rate. Because normative movement rate was individually matched to the previously observed average of self-selected task completion times, it is appealing to generalise that the 'ideal' movement rate emerged *as a result* of co-regulation between the two skill parameters. We might consider this as further evidence that error-based feedback is a necessary and significant factor in regulation of movement rates about an 'ideal' average in reciprocating reaching tasks, because motor skill is thought to arise through effective co-regulation between goal-oriented motor activity and sensory detection of the result in relation to the goal i.e. the degree of spatial error (Diedrichsen *et al.*, 2010).

A statistically significant difference in co-regulation behaviour between behaviourally manipulated conditions was found such that the alternate hypothesis for question 4 was accepted, providing further circumstantial evidence that co-regulation of movement rate and spatial error as a basis for motor control are found around a modulated, moderate movement rate. But the difference was only found between the speed-emphasis and normative conditions. Others have observed that, both in cyclic (Huys, Fernandez, Bootsma, & Jirsa, 2010) and discrete (Sleimen-Malkoun et al., 2012) reaching/targeting task, reaching kinematics were abruptly disturbed above a breakpoint level of target *difficulty*. This discontinuity was considered to be inferential of the interaction between the limitations of the neuromusculoskeletal system and the accuracy constraints of tasks (Sleimen-Malkoun et al., 2012). As already discussed, because time is required in order to incorporate corrective motor actions towards the target, on average this may be proportional to the extent of motor noise

in the control system (Meyer et al., 1988) which is perhaps the fundamental factor determining the outcome of skilled performance (i.e. precision)in manual tasks (Churchland, Afshar and Shenoy, 2006).

We did not observe significant systematic co-regulation between the outcomes inferential of movement rate and spatial accuracy during free practise. It has been considered that, in a non-perturbed, stable environment, on-line sensory information should become *less* important to spatial accuracy as the adaptive elements of the motor system are tuned to the environment (Shadmehr and Mussa-Ivaldi, 1994). Thus systematic error, which arises through mismatches between the estimated and actual end-effector (object) and target positions (Shadmehr, Smith and Krakauer, 2010; Missenard, Mottet and Perrey, 2009) is thought to be countered by the evolution of internal 'forward' predictive models for environmental interaction that is recalibrated through ongoing experience (Burge, Ernst and Banks, 2008; Kawato, 1999) via an estimate based both on immediate and historic sensory observations (Shadmehr et al., 2010). On the other hand, previous findings in respect of the importance of vision in aiming movements found that sensory feedback of both the target and hand position was important not only for learning of the skill but continued optimal movement accuracy in a spatially demanding task following learning (Proteau *et al.*, 1987). That is, the random component of error due to innate noise in the central nervous system (Churchland, Afshar, & Shenoy, 2006) must continue to be corrected for through on-line processes close to the target, although estimation of the magnitude of spatial corrections required may inform task learning and future performance (Worringham, 1991). Thus, both the accuracy of the forward model based on experience (Smeets *et al.*, 2006) and on-going feedback of performance (Sabes, Jordan and Wolpert, 1998; Proteau *et al.*, 1987) are critical to the total effect of noise on the outcome. The developing forward model mitigates the combined effects of motor noise and systematic planning errors, with the systematic component tending to zero over time (Shadmehr et al., 2010; van Beers, 2009) while the component of random variability remains (Burge et al., 2008).

Taken together, the behaviour observed under the normative condition may be predictive of a skill which is refined through experience, such that the speed-accuracy relationship acts to minimise the effect of random error on kinematic precision. As internal and external force environments governing systematic error are subject to change and an accurate knowledge of these is necessary for gain calibration of the sensorimotor system (Yarrow, Brown and Krakauer, 2009) the experience-dependent forward model may not remain stable between

successive practice sessions.These notions could be tested by the gathering of data using the current task over longer periods of experience.

3.8.5 Limitations of the study and methodological considerations

Though behavioural motivation was standardised in general, we cannot discount the effect of the consistent verbal instruction upon the outcomes. Group mean increases in movement rate were accompanied by increases in error scores over successive free practise sessions. This may be because the task instruction to volunteers influenced performance and the innate drive to increase completion time was more compelling than the desire to produce accurate placements. Alternatively, it could be that performance of the intervening behavioural manipulation blocks had the effect of disturbing the interrelationship between the speed of motor performance and observed spatial error in some fashion.

Significant differences in error distribution were found between the speed- and accuracy-emphasis conditions with a significantly greater proportion of errors occurring at the 0° target compared to the accuracy condition. That is, when participants were guided to reduce movement rate relative to the normative condition by 10% the ability to perform skilfully was detrimentally affected in relation to the most difficult targets. But the reason for the marked shift in greatest relative error from the 120° target to the 0° target, noted only in the speed-emphasis condition compared to the other 5 block conditions, is unknown but could perhaps arise as a result of an interaction between grasp kinematics and the parameters of the particular task. In accordance with Fitts' Law, there may also be a general conventional effect of target width on I_D but both factors (which are tied parameters in the standardised target design) probably interacted to produce the scaling of difficulty across the rail orientations which we infer from the above observations. Though this consideration does not alter the validity of the current results it may inform the design of future tasks. Note that limitations of this analysis apply, in that the TPR measure can only detect extents of spatial variability which actually result in an error score.

A strength of the MSRT task/measurement paradigm is that it does not have to be completed successfully to be valid: individuals are encouraged to evolve performance models empirically towards a motivational goal of maximising productivity ('as accurately/ as fast as possible') and so ceiling effects in the conventional sense applied to clinical outcome measures are theoretically not possible in relation to the TPR unless participant behaviour deviates radically from the simple verbal instruction provided throughout task practise. Rather than attempting to summarise motor skill by measuring a single parameter of behaviour, TPR measure exploits the capacity of the human motor system to manage performance based on experience of the

accuracy constraints. This approach has, in fact, recently been recognised in the literature as a means of reconfiguring Fitts' law based on the relationship between movement rate and spatial accuracy (Guiard and Olafsdottir, 2011). The inference, from the data gathered from performance in our procedurally easy but spatially challenging task, is that completion time and spatial error are simply components of skilful activity which summarise information conversion processes over time and are in isolation difficult to interpret in relation to the construct of practical motor skill. Replicating these findings in further studies observing behaviour in completing the MSRT under constrained movement rate conditions or over longer periods of experience may also allow researchers to make a distinction between sources of error and how these vary over time.

An unexpected observation was that, across successive practise blocks individuals appeared to voluntarily modulate performance strategies to conserve error rate and persist to working within a range of error throughout their study performance (Figure 3.9). A stable approach to spatial variability forms a simple basis for developing movement plans that does not depend upon extended periods of experience (Brenner and Smeets, 2011; Witney, Vetter and Wolpert, 2001). In sampling the outcome of what appear to be noisy processes across a range of target difficulties during each trial, we essentially produced a continuous measure of spatial variability on the basis of combined reaching and angular accuracy components, which together tested the net contributions of proximal and distal joint control to prehension ability (Wong and Whishaw, 2004).

The relative stability of the error score over successive practise blocks, which persisted in the final free practise block following 60 trials of behavioural manipulation, is consistent with the theory that skilled motor behaviour is at least partially modulated by feedback of goal success in a circular fashion (Diedrichsen *et al.*, 2010). Only one participant completed a totally error-free block of 20 trials, which occurred under a guided reduction of movement rate to simulate accuracy emphasis, while conversely floor effects (under which 100% error occur), though predicted and planned for (VII.2.9.4.8) were not recorded under any behavioural condition. In other words, when implementing a multiple I_D array of which the MSRT is an example, there appear to be minimum bounds upon spatial variability about an individual ceiling where movement rate and the error rate interact to result in a region of linearity.

The practical net outcome of motor learning, distinct from fast adaption, is to reduce kinematic variability in the trained task (Shmuelof, Krakauer and Mazzoni, 2012). The plan may be subject to improvement over time because increasing the history of somatosensory

experience might refine the model of the net effect of noise on spatial error (van Beers, 2009). But because spatial error itself is the product of random and systematic error, the former source of which is thought to be innate to the motor system (Burge, Ernst and Banks, 2008), it may be that volunteers selected a pragmatic strategy for corrective movements which reflects an individually acceptable level of error or, conversely, the capacity for spatial accuracy (Figure 3.9).

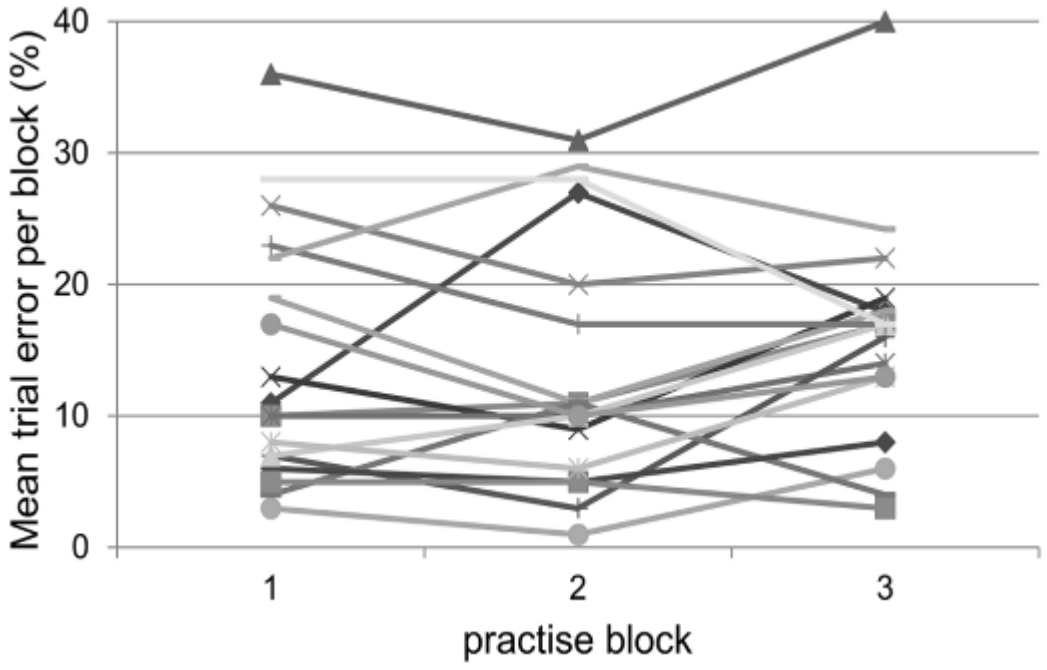


Figure 3.9: Absolute magnitude of spatial error rates is highly variable between subjects but approximately preserved within subjects over successive free practise blocks.

Mean aggregate trial error percentage per block by each of 18 participants, over 3 practise blocks. Each datapoint represents the arithmetic mean of spatial error over 20 MSRT trials, with lines linking successive practise blocks performed by a single subject.

3.9 Conclusions

This study was concerned with investigating the properties of a novel univariate outcome measure inferential of task-dependent motor skill learning. In contrast to highly significant changes in the component skill parameter of task completion time, the TPR measure was statistically stable over large perturbations in behavioural approach. On the basis of this finding, highly significant changes in the TPR skill measure found over successive periods of task practise were considered unlikely to be due solely to behavioural adaption and were therefore true reflections of skill learning, although statistically significant outcomes due to behavioural bias may arise to an extent depending upon the sample size or study design employed.

Altering rail target orientation was a reliable means of manipulating target difficulty during free task practise, constituting a reliable feedback condition against which movement rate might be modulated to improve performance in relation to the behavioural goal. Behavioural manipulation resulted in significant changes in error distribution and co-regulation behaviour between the skill parameters, providing evidence that even during practise of complex motor tasks skilled behaviour might emerge from direct observations of, and short-term response to, targeting error.

The constructs embodied by the TPR measure accord with Fitts' theories and can be related to previous findings in relation to the influences on motor control and learning. The univariate TPR outcome measure represents a quite simple approach to quantitative analysis of intervention-dependent changes in task-dependent skill which may reduce the effect of behavioural influences. MSRT trial measurements do not depend upon full targeting success as a prerequisite and therefore accommodates the abilities of humans with quite severe limitations in grasping and prehension abilities. The findings of the current study might inform the development of wide-spectrum measurement systems, to further unify findings in motor learning studies obtained from populations with diverse levels of physical ability. External validity and reliability should be further investigated by replicating the findings both in the healthy population and neurological populations.

Chapter 4. Study 2. Pilot study: effect of adjunctive anodal tDCS on retention of non-dominant upper limb skill learning and dexterity in chronic incomplete cervical spinal cord injured persons

4.1 Introduction

Cervical level spinal cord injury (SCI) disrupts sensory and motor pathways, impairing control of the upper limb and the extent of functional recovery (Darian-Smith, Burman and Darian-Smith, 1999). Tetraplegic patients value recovery of arm and hand function highly in attaining goals relating to quality of life, highlighting this as an important topic in rehabilitation research (Snoek *et al.*, 2004).

Neural plasticity underpins both healthy learning and rehabilitation from CNS injury, and is independent of pathology-specific issues such as sensorimotor impairment or spasticity (Warraich and Kleim, 2010). Indeed, recovery of movement after incomplete SCI occurs via a combination of functional compensation and neuroplasticity at multiple levels (Curt *et al.*, 2008). Functional and structural changes in the brain are associated with sustained increases in cortical excitability in the primary motor cortex (M1). In tetraplegic individuals upper limb task-oriented training which improves motor performance coincides with plastic increases in excitability of projections to involved muscles (Beekhuizen and Field-Fote, 2008).

It is possible to modulate the excitability of brain regions directly using non-invasive means, including transcranial direct current stimulation (tDCS) where small steady-state currents are applied to the scalp via electrodes (Nitsche *et al.*, 2008). When applied over motor cortex (M1) polarity specific changes in excitability are observed in evoked responses to transcranial magnetic stimulation: negative polarity reduces excitability of underlying neurons, while

positive electrode (anode) increases cortical excitability (Nitsche *et al.*, 2008). While tDCS is a relatively non-focal technique it is safe within known parameters and therefore has potential as a practical clinical application (Nitsche *et al.*, 2008). The application of anodal tDCS during learning tasks induces lasting improvements in functional outcomes in healthy (Reis *et al.*, 2009), and stroke-affected (Boggio *et al.*, 2007) subjects compared to sham stimulation protocols, underlining the behavioural relevance of stimulation paradigms which might also enhance the lasting benefit of motor rehabilitation in tetraplegics.

Observations and feedback from participants during training, as recorded in the laboratory log, suggested that cutaneous sensation, rather than motor preservation had an important bearing on the ability to perform the training task. There is a high association between the ASIA pinprick test scoring and recovery of skilled upper limb function in upper limb function in chronic SCI (Kirshblum and O'Connor, 1998). It has been suggested that the close physical proximity of the sensory lateral spinothalamic and efferent corticospinal tracts in the spinal cord limit the ability to improve in function over extended periods of time (Kirshblum and O'Connor, 1998). However, the crucial role of cutaneous and mechanoreceptors in joint stability and motor control are known in healthy physiology (Riemann and Lephart, 2002) and so may have a direct bearing on motor learning. A further post hoc analysis incorporating sensory scoring was used to control for this aspect of sensory sparing.

We hypothesised that anodal tDCS might significantly alter the lasting outcomes of motor training on task-specific learning, compared to a blinded sham tDCS condition. The skill-based outcome measure, Task Productivity Rate (TPR) was derived from practise in a sequential unilateral upper limb motor skill rehabilitation task (MSRT). We explored the cumulative, lasting behavioural effects of anodal tDCS on a generalizable valid measure of motor dexterity, the nine hole peg test (9HPT; Oxford Grice *et al.*, 2003) when applied adjunctively to training. Additional outcome measures were applied to measure upper limb functionality, with subtests of the Jebsen Taylor Hand Function Test (JTHFT) (Jebsen *et al.*, 1969) and pinch force, using a hand held dynamometer. As a secondary research topic we questioned the nature of the relationship between the 9HPT and TPR task-dependent skill outcome measure in order to test the null hypothesis that the TPR outcome does not have comparable content validity. Measures were taken at baseline, from the start and end of sessions on day 2, day 3 and also the follow-up session 7 days later. To control for prior skilled experience and elicit the most substantial experimental effect, all training and stimulation activities in the current study were applied to the non-dominant upper limb. In order to elicit the most substantial experimental

effect from a naïve state of motor skill, all training and stimulation activities in the current study were applied to the non-dominant upper limb.

4.2 Research questions

4.2.1 Primary research question

How does anodal tDCS, applied adjunctively during a massed practise rehabilitation activity, change functional performance in a time dependent fashion compared to the sham (placebo) condition? The null hypothesis was applied, that the effect of tDCS would not cause a significant difference in the primary outcome measure TPR at the follow-up session compared to the sham condition.

4.2.2 Secondary research question

Do changes in TPR outcome of MSRT practise validly represent changes in skill, as indicated by the strength of correlation with the outcome of the primary *validated* outcome measure? In other words, do the two measures have good convergent validity and therefore provide evidence for the sensitivity of the TPR outcome measure in this population? The null hypothesis was applied, that the Spearman's Rank Correlation Coefficient between the two datasets would not be significantly better than 0.

4.3 Methodology

Prospective, single-blinded experimental sham controlled study.

4.4 Methods and materials

4.4.1 Sample size

This was the first study to investigate anodal tDCS in tetraplegic SCI subjects, so it was not possible to estimate a desired sample size from the effect size found in previous studies. However, significant changes in both motor cortical excitability and functional outcome due to therapeutic intervention in SCI individuals (Beekhuizen, FieldFote2008), and adjunctive tDCS in stroke patients (Hummel, Celnik et al. 2005) have been demonstrated against sham controls in sample sizes of 6 per group. In healthy individuals, a crossover study involving eight subjects revealed the highly significant short term effects of anodal tDCS vs. sham on non-dominant arm motor skill performance (Boggio, Nunes et al. 2007). In order to minimise the probability of type II error and allow for dropouts, both intervention and control groups might constitute 6 to 8 individuals each. Based on the findings of previous studies, we made an a priori desirable total sample size estimate of 16.

4.4.2 Randomisation to groups

The method of randomisation and assignment, and the single blinding applied in Study 2 are discussed in SectionVII.2.11.5. Briefly, on study inclusion participants were allocated to active or sham control groups consecutively by pairs.

Table 4.1: Participant profile.

Clinical assessment at time of recruitment, with respect to left upper limb only.Participant descriptives. SCI=spinal cord injured/injury. Gender, F=female, M=male. Age in years. Time post-injury in months. ASIA=American Spinal Injury Association. Aetiology: T=traumatic, NT=non-traumatic. Hand score: modified version of the Edinburgh Handedness Inventory. Independent Mann-Whitney U comparisons testing null hypothesis that distribution of respective parameter is the same across groups.

Gender	Age	Time Post-injury (months)	ASIA AIS level classification	Aeti-ology (T/NT)	Hand score	Clinical assessment of the non-dominant upper limb, levels indicated		
						Motor score/25 C5-T1	Light touch/14 (C3-T1)	Pin prick/14 (C3-T1)
ACTIVE								
F	28	20	C5 C	T	+100	11	10	9
M	41	240	C5 C	NT	+ 78	13	5	9
F	50	36	C7 D	T	+100	18	13	6
M	68	92	C5 D	NT	+67	20	9	7
SHAM								
M	64	48	C5 C	T	- 100	17	7	9
M	47	37	C5 D	NT	+100	19	11	10
F	47	120	C5 D	T	+100	12	9	11
M	60	252	C6 D	NT	+100	9	8	7
M-W U p value	0.561	0.386	n/a	n/a	n/a	0.564	0.663	0.180

4.4.3 Protocol

On 3 consecutive days, participants undertook 45 minutes of practise with the non-dominant limb in the MSRT task, during the first 20 minutes of which active or sham tDCS was applied to non-dominant M1 (Figure 4.1). Apparatus and administration were as set out in SectionVII.2.11. The task was implemented as a form of therapeutic repetitive task training where continuous trials of each test were undertaken interspersed with short rest intervals to minimise fatigue effects. Standardised behavioural motivation was applied in the form of vocal instruction to work as accurately and quickly as possible.

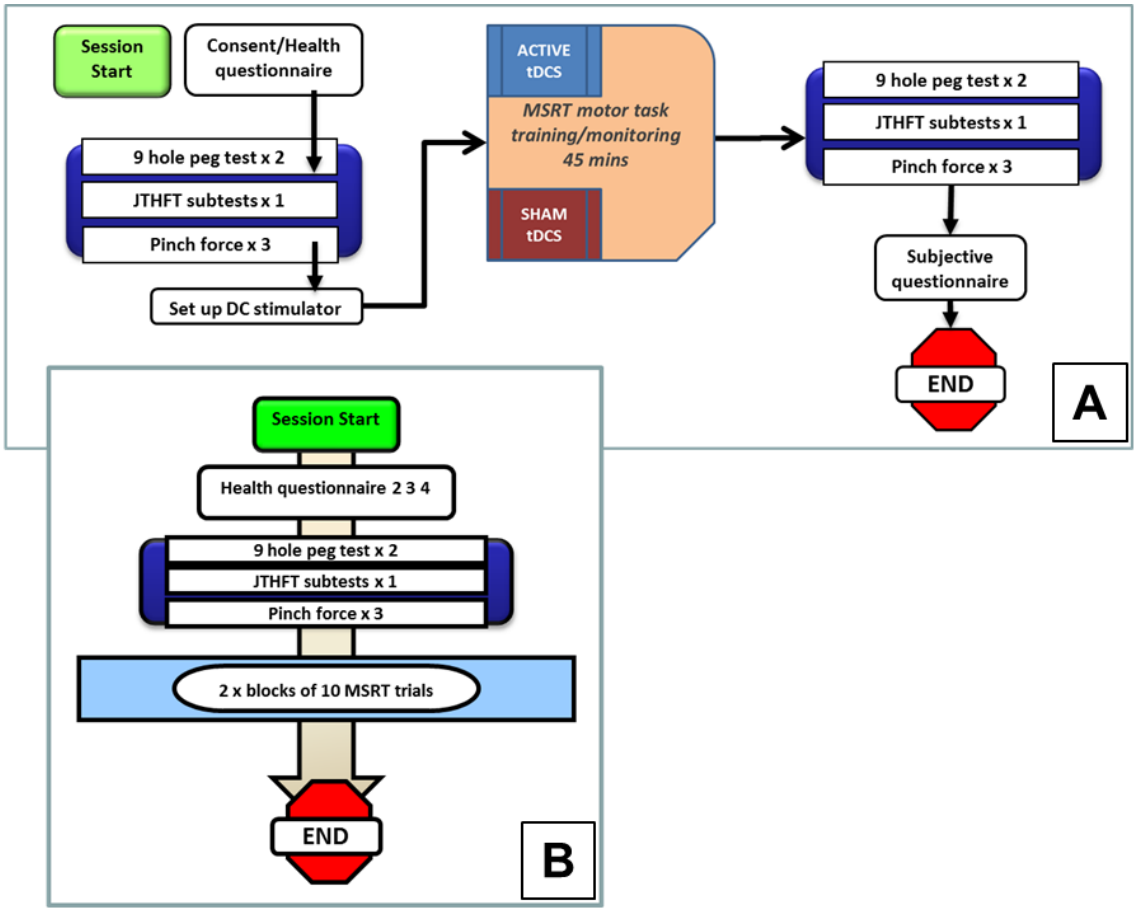


Figure 4.1: Schematic of study protocol for pilot Study 2.

A: Protocol for consecutive training days 1, 2 and 3. Active or sham tDCS were applied during the first 20 minutes of 45 minutes continuous MSRT skill task training. Behavioural outcome measures – 2 x 9 hole peg test, 1 x Jebsen Taylor Hand Function subtests and 3 x pinch force - were gathered prior to and following the MSRT practise period. Subjective questionnaires were also applied as part of health questionnaire prior to training and following stimulation/training on each day. B: Protocol for follow-up measurement session.

4.4.4 Standardised intervention dosage

1.0 mA active anodal tDCS or a sham control was administered to the scalp overlying the non-dominant M1 with single blinding, hardware and procedures over the first 20 minutes of each training session (VII.2.11.3).

4.4.5 Outcome measures

4.4.5.1 TPR - task-dependent skill measure

Completion time and residual spatial accuracy score were monitored concurrently during practise of the MSRT task used to calculate TPR (VII.2.9.4.6). The number of task trials completed during each training session differed markedly between volunteers, reflecting the heterogeneity of the sample in terms of baseline sensorimotor function. The TPR outcome was sampled from MSRT trial performances corresponding approximately to 15 minute periods from the start of each training session, as successive measurements inferential of task-dependent skill relative to the baseline value. This was considered to be a valid approach because learning is thought to be experience-dependent (Warraich and Kleim, 2010) and therefore tied to performance and exposure time rather than arbitrary numbers of trial repetitions (Eliassen, Souza and Sanes, 2003).

At follow-up, estimation of skill retention was made from the mean of 20 trials without prior practise. Due to consistently slow MSRT completion times, to reduce the incorporation of learning effects the mean of 10 trials was used to summarise the follow-up TPR score single participant in the group receiving active stimulation.

4.4.5.2 Validated functional measures

Functional measures were applied immediately prior to, and following each training session and at the follow-up session (Figure 4.1). Each was administered according to the standardised instruction. The tests were applied consistently in the following order:

- Two repetitions of the nine hole peg test (9HPT) (Oxford Grice *et al.*, 2003) repetitions were applied per interval. A time limit of 150s per repetition was applied.
- A single administration of the Jebsen Taylor Hand Function Test battery (JTHFT) (Jebsen *et al.*, 1969) was applied per measurement interval. The subtests of page turning, small objects, checker stacking, light cans and heavy cans were applied, being relevant to non-dominant upper limb function. Time limits of 120s per subtest were

applied. These 5 subtests were administered in order as dictated by a randomisation chart, and administered to the standardised instruction provided with the JTHFT.

- Lateral grip pinch force was measured as the mean of three attempts. A JAMAR-type lateral pinch force gauge was used.

Details of the apparatus and the literature supporting use of these measures are presented (VII.2.10).

4.5 Analysis

The aggregate JTHFT scoring was affected minimally by floor effects due to the range of prehension dimensions tested. TPR scores were not affected by floor effects as performance of the MSRT task was not subject to a task completion time limit. However, substantial floor effects were evident in the scores of both the 9HPT and pinch force tests at baseline and following intervals (Figure 4.2) such that the validity of the measures was considered to be compromised. Therefore, analysis proceeded using the JTHFT and TPR scores only.

All datasets were **block summarised** (see Section VII.2.14.1.1 for discussion of technique) and normalised relative to individual baseline values prior to analysis.

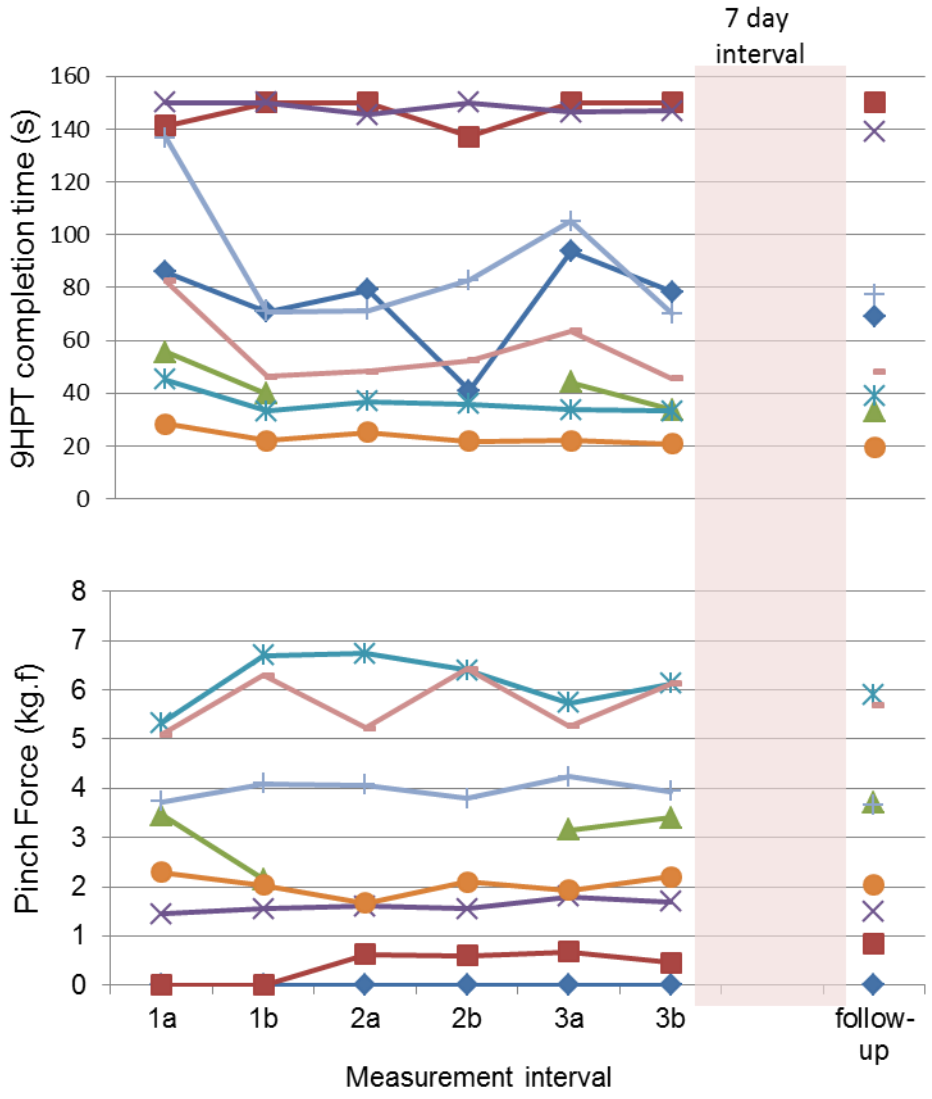


Figure 4.2: Floor effects observed in 9HPT and pinch force outcome measures.

Mean outcomes for each of 8 participants from repeated measures before and after 3 consecutive training /intervention days (a: pre-training, b:post-training) and a follow-up measurement session 7 days later. Nine hole peg test (9HPT): a time limit of 150s was applied per repetition. 2 of the total 8 participants had insufficient grasp strength to operate the pinch force gauge at baseline.

In order to address the secondary research question the JTHFT measure was adopted as the behavioural outcome measure, as the scores were not affected by floor effects.

A single participant in the SHAM group failed to attend the second practise session due to difficulties with transportation. Missing Value Analysis was applied following normalisation of the measures to baseline values, to generate values prior to analysis. Little's Missing

Completely at Random (MCAR) test was applied to test the assumption that the missing data points from the JTHFT and TPR datasets were indeed missing at random.

To investigate the primary research question, comparative analysis of the lasting effect of anodal tDCS on lasting retention of TPR and JTHFT behavioural outcomes were analysed across 4 intervals. Scores from the intervals prior to/at the beginning of sessions and at the follow-up measurement session were used for this analysis. The outcome datasets were normalised to individual baseline values and tested with repeated-measures, mixed-effects analysis of variance (ANOVA) with planned contrasts and generation of parameter estimates.

The contribution of pinprick sensory function to changes in the JTHFT and TPR outcomes was tested using mixed-effects analysis of co-variance (ANCOVA) with planned contrasts and parameter estimates. All assumptions for ANOVA and ANCOVA were tested for and found to be met, including those for homogeneity of variance and regression slope. In addition, the ANCOVA assumptions of validity in terms of regression slope homogeneity (Field, 2005) were tested via an additional custom ANCOVA to test the interaction between the co-variate and the group variable. This returned a between-subjects interaction effect of $F(1,4)=0.524$ $p=0.509$ demonstrating that the regression slopes of the variables were not significantly different, confirming that the assumptions of the ANCOVA analysis held for the analysis.

To investigate the secondary research question, the associations between raw JTHFT dexterity and MSRT performance scores was tested across 7 measurement intervals at the initial and final measures at each training session and at the follow-up session. Non-parametric linear statistical dependence was tested with Spearman's rank correlation coefficient and curve estimation also applied to characterise the curvilinear relationship between datasets.

4.5.1 Subjective tests

Standardised subjective tests of perception, in the form of numerical scale questionnaires(Appendix E) were applied at a total of 6 intervals, immediately following training sessions and at the beginning of the following session following provision of consent. See Section VII.2.5 for discussion of results.

4.6 Results

Baseline measures were highly variable between individuals but were not significantly different between intervention groups (Table 4.2).

Table 4.2: Absolute outcome measure values at measurement intervals, with separate independent t-test comparisons between baseline values.

JTHFT: Jebsen Taylor Hand Function Test battery aggregate time score of 5 subtests (s); TPR: Task Productivity Rate measure derived from MSRT practise task. Independent t-test group comparisons of outcomes across groups at baseline: t and p values for each measured parameter.

		ACTIVE		SHAM		Independent t test	
Outcome	**interval**	**Mean**	**SEM**	**Mean**	**SEM**	**t**	**p**
JTHFT	**Baseline**	198.3	106.9	92.7	31.6	0.947	0.380
	2	159.1	91.2	68.6	20.2		
	3	140.0	75.4	77.3	15.2		
	follow-up	138.1	81.2	77.5	28.6		
TPR	**Baseline**	29.94	21.12	7.88	4.21	1.023	0.346
	2	22.99	15.20	7.40	4.34		
	3	28.83	23.11	5.41	2.31		
	follow-up	13.60	9.01	8.71	5.66		

Table 4.3: Results from statistical tests on behavioural outcome measures.

Behavioural measures, JTHFT: Jebsen-Taylor Hand Function Test. TPR: Task Productivity Rate. ANCOVA: Analysis of covariance. For JTHFT ANCOVA analysis, the pinprick co-factor was shown to be non-significant therefore other comparisons were invalid and not reported. Between-groups test at 7 days: parameter estimates generated within ANCOVA models. *Significant between-groups difference at p≤0.05.

Behavioural measure		***JTHFT***			***TPR***		
	Main effect/interaction						***p***
TEST		***F value***	***df***	***p value***	***F value***	***df***	***value***
ANOVA	**INTERVAL**	12.084	3,18	<0.001*	3.923	3,18	0.026*
	GROUP	1.993	1,6	0.208	3.592	1,6	0.107
	INTERVAL*GROUP	3.225	3,18	0.047*	2.582	3,18	0.085
	Between-groups test at 7 days	*t=-1.869*	*6*	*0.111*	*t=-2.240*	*6*	*0.066*
ANCOVA	**PINPRICK**	0.060	1,5	0.186	6.919	1,5	0.047*
	GROUP	n/a	n/a	n/a	12.954	1,5	0.016*
	INTERVAL	n/a	n/a	n/a	0.600	3,15	0.625
	INTERVAL*GROUP	n/a	n/a	n/a	3.435	3,15	0.044*
	PINPRICK*INTERVAL	n/a	n/a	n/a	0.972	3,15	0.432
	Between-groups test at 7 days	n/a	n/a	n/a	*t=-3.159*	*6*	*0.025**

The results of comparative statistical tests are shown in Table 4.3. On the JTHFT outcome of generalized behaviour, there was a significant main effect of training across both groups. While the main effect of group allocation was not significant, there was a significant INTERVAL*GROUP interaction indicating that effects were modulated progressively to a significant extent in favour of those receiving ACTIVE tDCS stimulation. However, post-hoc testing showed that there was not a significant difference in scores between groups at any single time interval, including the follow-up session. The non-significant group-dependent effect size at follow-up, calculated from the t value t(6)=-1.869 p=0.111 was $r_{JTHFTlasting}$ = 0.610, with a mean 15% greater improvement for the active group in scores compared to the sham group at follow-up. Testing the effect of the PINPRICK test score on this outcome, rmANCOVA of JTHFT showed that the between-subjects factor of PINPRICK scoring did not have a significant effect upon the model.

Likewise, The ANOVA for TPR scores returned a significant cumulative lasting effect of practise between intervals across TIME. There were trends to significance with respect to the GROUP effect and INTERVAL*GROUP interaction in favour of ACTIVE stimulation at the follow-up session. Relatively greater improvements with an average 42% improvement in performance relative to the baseline condition, compared to 7% retained improvement in the group who received the sham stimulation condition. Acting on observations to take into account the effect of PINPRICK scores on retention of motor skill, the PINPRICK co-variate was shown to have a significant modulatory effect on the model which, furthermore did not interact with the effect of practise over successive sampling intervals, providing further validity for the analysis of this factor as independent.

The ANCOVA analysis returned a non-significant general effect of practise as an independent factor across the entire sample suggesting somewhat surprisingly that, when the effect of sensation was accounted for, practise was generally ineffective in modulating task-dependent motor skill over the duration of the study. Instead, group allocation had a significant modulatory effect on the capacity to perform the MSRT sequential target matching task. Contrasts showed that this interaction was significant at the follow-up sampling interval. Parameter estimate B values confirmed firstly that the effect of the intervention was beneficial (B=-0.475). Secondly, the effect of pinprick sensitivity upon the TPR outcome was also proportionally beneficial(B=-0.085) i.e. better sensory acuity in the non-dominant limb was associated with improved retention of task training.

4.6.1 Effect sizes and power calculations

Calculating effect sizes from parameter estimate t-values with df=6 showed that at the follow-up session the effect of PINPRICK, though not significantly responsible for the difference between subject's outcomes at this interval t(6)=-1.794 p=0.133, was moderate at $r_{pinprick}$ =0.349, while there was a large effect of group allocation on the between-subjects model t(6)=-3.159 p=0.025, r_{group}=0.625. From these r values, the factors of group allocation and sharp-blunt acuity accounted respectively for R^2_{GROUP}=35% and $R^2_{PINPRICK}$=12% of the variance in retention of task-dependent skill between subjects.

In order to determine the minimum number of subjects per group to detect a significant between-groups difference in the TPR outcome measure, from the data of pilot Study 2, Equation 2.15-2 was applied as the sample size calculation. The effect size d_{TPR} at the follow-up session, for independent data with differing standard deviations was first calculated (Equation 2.15-3).

Means: active = 0.580; sham = 0.927

Standard deviations: active = 0.184; sham = 0.249;

Then $d_{TPR}= \frac{0.927-0.580}{\sqrt{\frac{(0.249)^2+(0.184)^2}{2}}} = \frac{0.347}{0.219} = 1.584$

And from Equation 2.15-2, $n = \frac{15.7}{d^2} + 1 = 7.25$.

Therefore, 7.25 = 8 persons per group would be required to detect a significant between-groups difference in the TPR outcome measure with statistical power 1-β 80% and level of significance α equal to 5%. It is notable that the value of d = 1.584 is considered to be an extremely very large effect size according to Cohen (Cohen, 1992) who regarded a value of d = 0.8 as large. This result also suggests firstly that our initial sample size estimate was accurate, but also confirms that the study was also substantially underpowered.

Investigating the secondary research question, the 54 raw paired JTHFT and TPR scores were compared. Improving motor dexterity in the aggregate JTHFT outcome is indicated by reduction in time score, while improving TPR motor skill is also realised by diminishing scores (s/score). Visualisation of the data suggested a non-linear relationship between the datasets. A strong linear association (Spearman's ρ =.908(54) P<.001) was found between absolute values of the novel TPR and JTHFT outcome measures. The association between the test distributions was tested against logarithmic, power and exponential regression models by curve estimation.

Visualisation of the data revealed a non-linear association between the outcomes, however (Figure 4.3).

Curve analysis with TPR as the independent variable revealed a strong power association [JTHFT] =26.117[TPR]$^{0.6}$, with coefficient of determination R^2=0.931(54) and significance p<.001 (Table 4.4).

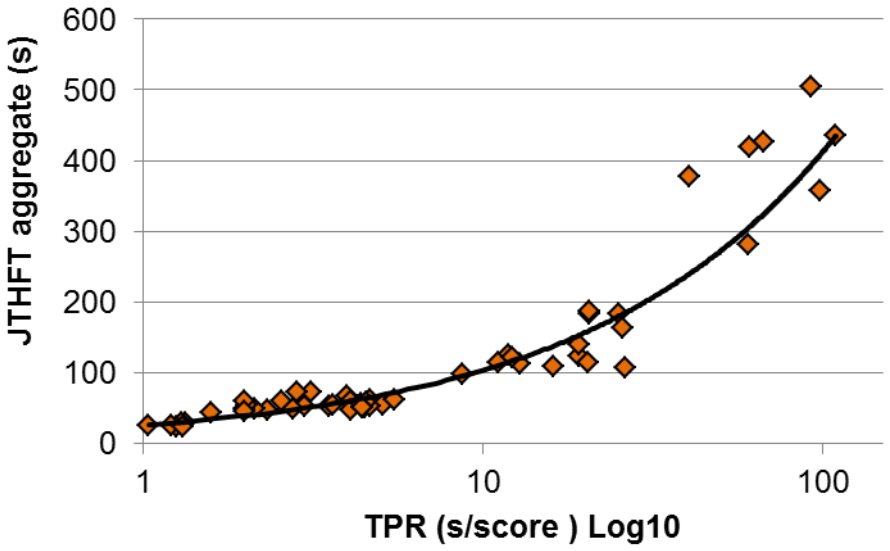


Figure 4.3: Strength of association between TPR and JTHFT outcome measures from all subjects and intervals, N=54 data points.

Abscissa scale shown in Log10 format for clarity. Power trend line [JTHFT] =26.117[TPR]$x^{0.6}$ R^2=0.931, p<0.001.

Table 4.4: Curve estimation model summaries and parameter estimates.

TPR as the independent variable and JTHFT as the dependent variable. Coefficient of determination, significance and parameter estimates. Significant at **p≤0.001

model	R^2	F value	Df	P value	constant	Exponent/base
Logarithmic	0.772	176.460	1,52	<0.001*	-38.597	81.888
Power	0.931	698.675	1,52	<0.001*	26.117	0.600
Exponential	0.730	140.728	1,52	<0.001*	52.847	0.027

4.7 Discussion

4.7.1 Main findings

The 9HPT outcome measure lacked sensitivity in the study sample of convenience, while the JTHFTand so the JTHFT measure was substituted as a valid measure of dexterity.

The primary research question was applied to the results of the TPR dataset analysis. We found a significant between-groups difference between TPR scores at the follow-up interval, but only when a predictive factor was included in the analysis, and so there was insufficient evidence to reject the primary null hypothesis.

The secondary research question asked whether, in order to test the sensitivity of the novel TPR outcome measure against a valid measure of upper limb function, there was a significant association between the datasets of the two measures. We found excellent and highly significant, excellent correlations, both in terms of non-parametric linear association between the ranked datasets and a non-linear association between the paired datasets. We concluded that there is sufficient evidence to accept the alternate hypothesis, that the TPR outcome measure carries comparable validity as an outcome measure in the study sample.

4.7.2 Comparison of changes in JTHFT and TPR datasets

In a set of tasks which together assess effectiveness in grasp and transportation strategies, but do not apply spatially challenging end points (JTHFT), anodal tDCS interacted with ongoing practise to a significant extent. However, in the training task where grasping and transport was simplified and standardised but the spatial goals are challenging, as in the MSRT task, we only found a similar trend in the TPR skill outcome measure.

An associative analysis indicated that, while the relationship between the two measures was excellent, TPR appeared to capture additional factors of upper limb functional capacity compared to the JTHFT scores. The relationship was best represented by a power function which suggests that the TPR measure was sensitive to additional dimensions relating to motor deficit.

The 5 subtests of the JTHFT task battery present a range of different object grasp and transport challenges but do not present a stringent challenge to target accuracy, while the MSRT sequential task presents a stringent challenge to spatial orientation and placement of objects

which are easy to grasp. Recognition of these essential differences between the sequential tasks involved in these measures, coupled with observations and verbal feedback from participants recorded in the lab log led us to consider sensory sparing as a possible predictive factor for motor skill learning (as distinct from baseline dexterity capacities).

4.7.3 Effect of sensory sparing on capacity to learn motor skills

When sensory ability to discriminate between pressure focality was considered as an independent factor in task success and included as an additional factor in the analysis, a significant effect on the task-dependent outcome was revealed at the follow-up session. In fact, at the follow-up session the between-subjects interventional factor of group allocation and co-factor of sharp-blunt acuity were shown to contribute respectively to approximately one third and a tenth of the variance in task-dependent skill improvement. The contribution of sensory function to task-dependent motor learning is plausible in general. It has been found that, both in neurologically-impaired and healthy persons the ability to complete tasks including manipulation of small objects is highly correlated with measures of light touch pressure sensation (Melchior, Vatine and Weiss, 2007). Sensory inputs are known to be a powerful facilitator of cortical reorganisation and functional improvements in dexterity of healthy humans (McDonnell and Ridding, 2006) and recovery from SCI in humans (Beekhuizen and Field-Fote, 2008) and experimentally lesioned animal models (Martinez *et al.*, 2009). Perturbation of the closely adjacent primary S1 with repetitive TMS during motor practise has a direct effect on the capacity to learn practical tasks (Platz *et al.*, 2012a) including spatial tracking (Vidoni *et al.*, 2010) which may be attributable to the impaired capacity to construct accurate forward models (Vidoni *et al.*, 2010).

Associative studies link ASIA sensory scoring parameters with recovery of functional independence in this population. In particular, there is a high association between the ASIA pinprick test scoring, which evaluates discrimination between sharp and blunt pressures, and recovery of skilled function in activities of daily living in upper (Spooren *et al.*, 2008; Poynton *et al.*, 1997; Ishida and Tominaga, 2002) and lower limb (Oleson *et al.*, 2005; Katoh and El Masry, 1995) motor incomplete SCI persons.

The strong relationship between pinprick scoring and functional independence following SCI has not been fully explained. Pinprick scoring is sensitive to the extent of sparing of spinothalamic sensory tracts (Poynton *et al.*, 1997). There is a close proximity between the afferent lateral spinothalamic and efferent corticospinal tracts in the spinal cord (Kirshblum

and O'Connor, 1998; Katoh and El Masry, 1995). It has been suggested that the sensory deficit is simply an indicator of damage to those physically associated motor fibres which limit the ability to improve in physical independence over extended periods of time (Poynton *et al.*, 1997).

However, the role of cutaneous as well as articular mechanoreceptors in joint stability and control are known in healthy physiology (Riemann and Lephart, 2002). Our results suggest that, in tetraplegic persons as in healthy individuals, sensory acuity is important as an independent factor in achieving experience-dependent skill improvements in spatially challenging motor tasks. Furthermore, and lending further substance to the relevance of investigating sharp/blunt discrimination as an independent factor in motor learning, we found no variation of the effect of ASIA pinprick scoring over time. This finding is a consistent with the theory that the burden of sensory deficit places an intrinsic limitation on learning of manual tasks, because the formation of sensory prediction models depends upon sensory awareness of error (Izawa and Shadmehr, 2011). Furthermore, we established that there was no interaction between the effects of the intervention and the effect of sensory scoring on TPR outcome scores, a finding which validates the analysis based on the assumption of independence of the between-subjects factors. However it also suggests that anodal tDCS was unable to have an effect on the limitations on motor learning imposed by sensory deficit.

Significant time- and intervention-dependent interaction effects were found upon both JTHFT and TPR outcome measures. But, while the relative improvement in JTHFT generic dexterity by the ACTIVE group was progressive the specific beneficial effect of anodal tDCS on the TPR outcomes of the spatial targeting task appeared to be delayed, with no material difference between mean scores until the follow-up session. This effect has not been observed previously in studies involving healthy persons or patient groups. However, we recognise that no published works have implemented a behavioural outcome measure similar to the TPR, which is capable of accounting for the interaction between movement rate and spatial goal accuracy as contributors to practical motor skill. Taken together with the more straightforward effects upon the completion time of the JTHFT outcome we consider that the unexpected effect on the TPR outcome is likely to result from the demonstrated sensitivity of the latter task outcome to deficits in target matching. Considering that the primary effect of anodal tDCS on cortical excitability is short-lasting, this suggests that there may be a more complex interaction of effects contributing to the ability to achieve spatially demanding goals which resolve over different timescales.

We established that the JTHFT outcome was not significantly affected by pinprick sensitivity and that the task is chiefly an aggregate test of speed in achieving grasping strategies and transportation of objects of different sizes and weight. Conversely, while both tasks superficially measure sequential grasping, transportation and object release capability over time, the MSRT task is concerned with target matching accuracy rate using standardised items which minimise the requirement for grip strength and lifting capacity. Once again, although not significant, it is insightful to consider the implication of the improvement in the JTHFT outcome in the active group relative to those receiving the sham intervention.

Many of the studies showing significant benefits of anodal tDCS upon motor outcomes apply clinical outcome measures in a slightly different way to the method applied in the present task. These involve training in a task to a near-stable level, measuring ability in the task at a baseline level and then re-testing performance in task repetition following the intervention (Sohn, Kim and Song, 2012; Hummel *et al.*, 2010; Boggio *et al.*, 2006a), which therefore measures the effect of anodal tDCS on improvement in performance independent of experience-dependent learning. We applied only one repetition of the JTHFT per measurement interval, without pre-training in order to assess the differential learning effect upon this valid clinical measure of upper limb dexterity free from previous task experience. Thus, both the JTHFT and TPR outcomes measure the adjunctive effect of tDCS upon motor learning. But because experience of the JTHFT was very limited, the JTHFT subtest tasks were not trained and so we would be unlikely to see a substantial experience-dependent learning effect. Putting aside the possible effects of bias, the results suggest either a substantial degree of skill transference from the trained task, or an effect of the intervention which is independent of the trained skill itself.

4.7.4 Possible underlying mechanisms

Following injury to spinal tracts, there is a lasting attenuation of excitability in related areas of M1, an effect reversed during the recovery process (Jurkiewicz *et al.*, 2007) which is primarily contingent upon functional reorganisation of surviving sensory and motor pathways to achieve behavioural adaption (Curt *et al.*, 2008). Likewise, functional improvement in SCI rehabilitation is associated with increases in focal M1 excitability (Beekhuizen and Field-Fote, 2008). Conversely, increases in contralateral cortical excitability in M1 are linked to short-term improvements in hand function in healthy persons (Sohn, Kim and Song, 2012) with lasting benefits in stroke survivors (Boggio *et al.*, 2007).

The known primary effect of anodal tDCS upon cortical excitability, when applied adjunctively during rehabilitation activities, might enhance behavioural adaption and the retention of practised skills. The primary short-term effect of anodal tDCS upon excitability of intracortical circuits in the M1 area underlying the anodal electrode pad (Lang *et al.*, 2005; Nitsche *et al.*, 2005) can also impact upon activity over wider areas of the brain. Positron Emission Tomography (PET) scanning has shown that, at rest increases in the activity of cortical and subcortical occur after anodal tDCS – in particular the regions of the stiatum and thalamus (Lang *et al.*, 2005), which may be related to increased glucose metabolism in the brain (Binkofski *et al.*, 2011). Co-activation between the ipsilateral thalamus, caudate nucleus of the striatum and M1 occurred at rest following anodal tDCS application (Polanía *et al.*, 2011). Furthermore, coupling of the caudate nucleus with the posterior cingulate cortex (a region associated with resting, or default mode states) was reduced but increased with the superior parietal cortex, a region thought to be important during visuo-motor integration (Reichenbach *et al.*, 2011). This convergent evidence suggests that anodal tDCS has a facilitatory effect on multiple motor networks concerned with the adaptation (Romanelli *et al.*, 2005), performance and learning of motor skills (Ma *et al.*, 2010; Doyon and Benali, 2005).

While acute recovery of function seems to involve activation of bilateral M1, functional plasticity of the contralesional M1 is associated with pre-motor cortex (PMC) activity in skill learning in more chronic SCI cases (Nishimura *et al.*, 2007). In experimentally lesioned SCI primates, electrophysiological recording of local field potentials at M1 and EMGs from target hand and wrist muscles has shown that post-lesional coactivation of antagonistic hand and upper limb muscles for dextrous upper limb tasks was accompanied by gamma-band intermuscular oscillation couplings not observed in the pre-lesional state (Nishimura and Isa, 2008; Nishimura *et al.*, 2007). Such adaptive plastic changes in functional connectivity are reminiscent of those found following limited experimental lesioning of the cerebral cortex (Darling, Pizzimenti and Morecraft, 2011).These benefits might also cascade down to the reinstatement of dextrous synergies in incomplete cervical spinal cord injury which, as our results suggest took place in the current study may be an alternative pathway by which generalisation of learned performance out to non-trained tasks takes place (Musienko *et al.*, 2012).

Thus, taken together with previous findings in relation to the known facilitatory effect of anodal tDCS upon cortical activity there are grounds to consider the potential for anodal tDCS to improve the activation of brain circuits important in the rehabilitation of upper limb

function from cervical level spinal cord injury. Improvements in the functionality of muscles in tetraplegic SCI subjects during recovery occurs concomitant to changes in cortical activation towards the healthy control state (Jurkiewicz *et al.*, 2010). However, anodal tDCS might have the capacity for even more remote effects in the CNS. Anodal tDCS has also recently been associated with a modulatory effect on interneuron activity at the cervical (Roche *et al.*, 2009) and lumbar spinal level, providing further evidence that brain stimulation modalities could have a plastic effect upon the activity of distributed neuronal networks both up and downstream from the stimulation site. This appears to be a feasible hypothesis because spike-timing dependent plasticity has previously been driven at the spinal level by temporally associating TMS single pulses with antidromic peripheral stimulation, to vary evoked EMG and force output bidirectionally (Taylor and Martin, 2009). This is of interest because patients exhibiting spasticity demonstrate relative loss of disynaptic inhibition compared to those with normal tone or flaccid paralysis (Nakashima *et al.*, 1989) suggesting that anodal tDCS application enhances at least short lasting disynaptic inhibition by modification of spinal network excitability (Roche *et al.*, 2009) which might be achieved by enhancement of corticospinal tract activity. Perhaps modification of the spontaneous discharge rate observed in animal (Purpura and McMurtry, 1965) and humans (Nitsche and Paulus, 2000) can, via intermediate mechanisms induce increased plasticity of networks at the spinal level.

4.7.5 Non task-specific effects

The findings suggested that at least part of the quantitative benefit of the intervention may be non-specific to the trained task, and therefore not directly related to skill. Anodal tDCS has been shown as significantly beneficial upon motor outcomes in other conditions and states where the component factor of muscle weakness, as well as agonist-antagonist co-contraction may, independently or together, affect upper limb functioning and ability, including stroke (Chae *et al.*, 2002; Bolognini *et al.*, 2011) Parkinson's disease (Cano-de-la-Cuerda *et al.*, 2010; Fregni *et al.*, 2005a) and ageing (Clark and Fielding, 2012; Hummel *et al.*, 2010). Muscle strength, by virtue of behavioural adaption may not affect skilled reaching behaviour per se (Hoffmann *et al.*, 2006) but the effects of muscle weakness alone on functional capacity and independence (de Vargas Ferreira *et al.*, 2012) can result in muscle fatigue presenting in a prominent qualitative lifestyle management issue in the chronic phase following SCI (Hammell *et al.*, 2009).

The limitations of current clinical motor performance outcome measures, in terms of the limited sensitivity to spatial outcomes have been discussed (VII.1.8.1). Furthermore, there is evidence that anodal tDCS can primarily enhance motor output over the short term when outcomes on muscle force (Tanaka *et al.*, 2011) or endurance (Cogiamanian *et al.*, 2007) are applied. Short-lasting maximum voluntary contraction of a hand muscle during tDCS stimulation interacted significantly with polarity effects upon cortical excitability (Thirugnanasambandam *et al.*, 2011), a finding which could be interpreted as a primary effect on metaplasticity at the systems level (Thirugnanasambandam *et al.*, 2011). Alternatively, the effects of anodal tDCS on strength-related outcomes could be due to direct facilitation of corticomotor excitability or altered synergistic or agonist/antagonist couplings, for example (Cogiamanian *et al.*, 2007). However, the effects on force outcomes have only been shown to operate over the scale of minutes which would further necessitate some sort of learning process in order to have a lasting impact upon behaviour.

4.8 Limitations of the study

4.8.1 Limitations of the outcome measures

Two outcome measures applied in this study were insensitive to change in participants exhibiting poor functionality in hand dexterity and pinch force, which provides some valuable insights. Firstly, that the study sample was highly heterogeneous, although the sample was not significantly unbalanced across the factors tested. Secondly, that the JTHFT was *not* insensitive to change in the study sample, but possibly at the expense of dimensions of functional capacity to which the TPR measure was sensitive. These observations reinforce an important issue with outcome-based clinical outcome measures in general. Whereas measures such as the JTHFT have wide applicability over a wide spectrum of functional capacities, it is partially because spatial goals are not stringently applied. Conversely, the close tolerances between the peg and hole targets in clinical measurement of the 9HPT, coupled with the recessed nature of the targets presents in a complete intolerance of target error, result in floor effects.

As a possible source of measurement bias, the co-variate factor of sensitivity to sharp and blunt (pinprick) stimuli at key dermatomes is a reliable and standardised part of the AIS measurement protocol (Furlan *et al.*, 2008). The assesse differentiates between pressure types (normal compared to sensory reference at a level above the injury: grade 2), the sensations feel qualitatively different compared to reference sensations established on the face (grade 1)

or if the individual cannot distinguish consistently between pressure types (grade 0). However, this interval scale measure is relatively coarse and, as applied in the present study from the assessment of 7 dermatome levels C3-T1 returns a 15 point scoring in the range 0-14. On the other hand, the coarseness of the scale improves the reliability of the measurement system, as responses are easy to interpret and score accordingly.

The JTHFT completion time of one subtest exceeded the stipulated time limit of 120s during the first session, for one participant in the ACTIVE intervention group. This scoring method was therefore insensitive to the full extent of average performance improvement for the ACTIVE group, hence biases the results in favour of statistical non-significance.

There is a limitation of the TPR outcome measure in the context of the current study population. Because of the large variations in baseline capability between individuals, samples constituted periods of time approximating to 1/3 of the session duration. Hence, the baseline sample captured mean TPR scoring over approximately 15min of practise during which the intervention modality was applied. While the background validation study for this outcome indicated that motor skill evolves slowly over extended practise time, the difficulty in measuring motor learning, which is a time dependent construct, might underestimate the effect of the intervention on TPR scoring. Instrument bias might therefore also apply to the results.

4.8.2 Other possible sources of bias

Selection/Non-respondent biases: there may be important differences between those included compared to those not included in the study. Based upon the finding of no significant differences between groups in terms of physiological parameters or baseline outcome scores, we believed that by good fortune the two intervention groups were well-matched. However, the finding that ASIA pinprick scoring was a significant variable on between-groups MSRT task performance indicates that the complex interaction of factors can only be truly controlled for by by stratified random selection from a large population that meets the inclusion criteria.

Proficiency (intervention) bias: The unfortunate failure of a participant to attend the second of three training sessions. It is uncertain whether, because of the apparent short-term, fatigue-like effect which affected participants to a variable degree, this individual performed better or worse than he might otherwise have done if he had attended all 3 sessions on consecutive days. Missing Value Analysis is an accepted means of addressing this problem (Schafer and Olsen, 1998) and was applied in the current study.

Expectation bias: because, for practical purposes the investigator could not be blinded to group allocation it may be that outcome scoring erred in favour of the active treatment group. It should be noted that while time scoring of the MSRT is participant-triggered, spatial accuracy is recorded manually.

4.9 Conclusions

This pilot study investigated the lasting effects of non-invasive DC brain stimulation upon lasting retention of learned motor skill in tetraplegic SCI adults. Significant between-groups differences in the motor skill outcome were found at the follow-up interval 7 days following training, but only when a further co-variate of sensory sparing was included. Hence there was insufficient evidence to reject the null hypothesis. The secondary alternate hypothesis, that the novel TPR skill measure has good convergent validity with the JTHFT measure of hand dexterity, was proven. Curve analysis additionally provided evidence that TPR may confer more information, hence is a more sensitive dependent measure of differences in dexterity than the JTHFT.

Comparisons of the effect of the intervention upon task-dependent skill against changes in the un-trained skill measure (JTHFT) suggest firstly that there may be an interaction of effects over different time scales in a task where target matching is important. Secondly and more importantly, the results hint that the lasting effect of anodal tDCS may not be primarily skill dependent. The importance of predictive factors upon the capacity for motor rehabilitation has also been highlighted, but which also serves to stress the need for larger sample sizes to control for the possible effects of population heterogeneity to statistically bias the results.

The results do, however, suggest the potential for adjunctive use of anodal tDCS in upper limb skill learning in rehabilitation activities. In addition, they provide a further insight into the mechanisms underpinning the effect of anodal tDCS on motor functioning in humans. Further studies including larger, more homogenous sample sizes and incorporating neurophysiological outcome measures should investigate the effect of anodal tDCS upon outcome measures reflecting practical behavioural goals and associated effects upon corticomotor plasticity.

Chapter 5. Study 3. Effect of adjunctive anodal tDCS on retention of spatial motor skill and corticomotor plasticity in healthy adults

5.1 Introduction

The current state of knowledge is that application of small, direct current to the scalp over M1 during motor training, known as transcranial direct current stimulation (tDCS) is associated with significant short-lasting polarity-dependent (Nitsche *et al.*, 2005) modulations in parameters of brain activity (Stagg *et al.*, 2012; Jang *et al.*, 2009) and cortico-spinal excitability (Boros *et al.*, 2008; Nitsche *et al.*, 2007) in human subjects. A number of blinded studies have also suggested that long-term significant enhancement of motor skill is possible and due to adjunctive application of anodal tDCS (Bolognini *et al.*, 2011; Reis *et al.*, 2009; Boggio *et al.*, 2007), which might amount to a practical adjunctive intervention to improve the effect of motor rehabilitation in the clinical setting (Tanaka, Sandrini and Cohen, 2011).

Clinical rehabilitation from motor impairment is fundamentally concerned with the lasting reinstatement of practical motor skills, where a motor skill is the ability to plan and execute a movement goal (Krakauer, 2006). To satisfy the requirement for an integrated motor learning task and measurement tool, a novel sequential motor task, which we term as the Motor Skill Rehabilitation Task (MSRT), was developed in consultation with healthy and tetraplegic volunteers and validated in Study 1 as a combined means of training and observing the formation of a novel motor skill from the naïve state. The TPR outcome measure satisfies the primary design criterion, which is to quantitatively capture the relative ability to achieve a standardised practical spatial goal over a limited period of time. In Study 2 we investigated the lasting effects of non-invasive DC brain stimulation upon retention of a trained spatial motor skill, and generalizability to untrained behavioural measures in tetraplegic SCI adults. There were issues relating to the heterogeneity and size of the sample which may have contributed to statistical bias and limited the generalizability of the findings. But the results suggested that there is the potential for adjunctive use of anodal tDCS during learning of upper limb rehabilitation tasks. But the findings of the pilot study also suggested that there may be an

interaction of effects over different time scales and that the lasting effect of anodal tDCS may not be primarily skill dependent. It was concluded that in order to investigate these findings further, studies including larger, homogenous sample sizes and incorporating neurophysiological outcome measures should be included, to investigate the effect of anodal tDCS upon outcome measures reflecting practical behavioural goals.

Complex prehension tasks of the upper limb are reliant on ensemble activations of proximal and distal muscles, which underlie a potentially limitless manifold of motor strategies that address the behavioural aim of achieving the spatial strategy with varying levels of success (Muller and Sternad, 2009). The practical net outcome of motor learning, distinct from fast adaption, is to reduce kinematic variability in the trained task (Shmuelof, Krakauer and Mazzoni, 2012). The M1 area of the brain is thought to be key to the encoding of spatial end-points, which are subject to dynamic, experience-dependent processes of refinement and maintenance (Stark, Drori and Abeles, 2009; Graziano, Taylor and Moore, 2002). As a secondary hypothesis we questioned whether the net experimental effect of the intervention and task practise might have a lasting effect upon the strength of connectivity between M1 and representative muscles of the shoulder and hand involved in the prehension activity. Changes in resting MEP SRc evoked from hand muscles have been associated with improvements in motor skill (Pascual-Leone *et al.*, 1995b). TMS-evoked neurophysiological measures were applied at baseline, immediately after the completion of the two day protocol and at follow-up a week later in order to examine the short-term and lasting effects of the intervention on these inferential measures of neuroplasticity. Single and twin-pulse transcranial magnetic stimulation (TMS) measurement protocols were applied to measure resting and active stimulus-response characteristics (SRcs) from the abductor pollicus brevis (APB) and active SRc from the medial deltoid (mDelt) muscles.

5 subtests of the Jebsen Taylor Hand Function Test, a commonly utilised functional test in behavioural studies, were applied to test for lasting changes in generalizable motor function. In addition subgroups of subtests have been used to respectively to highlight differences in gross-motor proximal and fine-motor distal functioning (Hummel *et al.*, 2005). Subjective questionnaires gathered information relating to the efficacy of the double-blinding procedure.

5.2 Research questions

The research questions reflect the aims of the study, which are to investigate the effect of adjunctive tDCS on lasting development of a new motor skill and associated neuroplasticity from the naïve state.

5.2.1 Primary research question

Is there evidence of lasting changes in the development of motor skill, detected from the sampling of the TPR behavioural outcome measure attributable to the application of anodal tDCS? The alternate hypothesis applied was for a statistically significant lasting difference to exist between ACTIVE and SHAM group mean TPR measures at the follow-up interval.

With the aim of investigating the effect of the intervention on control strategy which supported skilled enactment of the motor task, the state of co-regulation between the skill parameters of task completion time and error rate which underlie the TPR behavioural skill measure was analysed and compared between groups at each measurement interval. For the same reason, the distribution of error scores across the array was also analysed.

5.2.2 Secondary research question

Is there evidence of associated significant changes to parameters of primary motor corticospinal excitability associated with upper limb prehension, attributable to the application of anodal tDCS? The alternate hypothesis applied was for a significant between-groups difference in group mean resting APB MEP area recruitment curve parameters to exist between the ACTIVE and SHAM groups means as defined above, at the follow-up session.

5.3 Methodology

Prospective, double-blinded experimental sham controlled study.

5.4 Methods and materials

5.4.1 Sample size

The primary research question was focused on experimentally determining the lasting effect of the intervention upon behaviour, detected from TPR skill scores at follow-up relative to the baseline score. From Study 2 a sample size of n=8 per group was calculated as adequate to

reject the null hypothesis. It was considered a possibility that the lasting effect of the treatment in the healthy population after 2 training intervals in an identical task would be less marked than that found in the patient group following 3 training intervals. On the other hand, we might expect the variability of outcomes (that is, the mean standard deviation) in this relatively homogenous population due to unknown confounding factors to be less, which may assist in bringing any effects of anodal tDCS further into relief. Hence though determination of sample sizes was somewhat speculative based on the limited information, the pilot study suggested that the *order* of total sample size which may be required to demonstrate statistically significant effects, if they existed, to be 16-20.

This is a sample size commensurate with tDCS studies utilising TMS as an outcome measure (9, crossover design) (Galea and Celnik, 2009) and short-term (Kang and Paik, 2011) (11, crossover design) and lasting (Reis *et al.*, 2009) (12 per group, parallel experimental design) performance change due to adjunctive anodal tDCS application. Significant findings have also been made in relation to the effect of this intervention with 10 per group (crossover design) (Hummel *et al.*, 2010) using JTHFT outcomes as the inferential measure. The target sample size was initially fixed at 20 participants, with a successful programme of recruitment leading to an ethically-approved increase to 24 participants.

5.4.2 Participant recruitment and allocation

Ethical and participant recruitment procedures for this study were as laid out in Section VII.2.2.

Participants were recruited as previously discussed (VII.2.2).Inclusion criteria for this study were for age range 18 and older, male or female and right hand dominance. Those applicants who reported pregnancy; histories of poor short or long-term health status, in general and in particular relation to head injury, stroke or seizure; neurosurgery to the head and/or implantation of metal objects such as metallic plates or aneurysm clips to the head; cardiac conditions; internal prosthesis or implant anywhere in the body or current dermatological conditions were excluded.

A single participant dropped out of the study following one session, citing an acute medical condition unconnected with the study. The data arising from this participant was disregarded from analyses. A replacement volunteer was recruited and undertook full participation.

The full datasets from 24 healthy adults (9 females, 15 males; age: median 23.5; range 18-42) are included in the analyses of the current study. These persons were recruited from the staff

and student body of Brunel University London by open advertisement. All considered themselves right-hand dominant and confirmed this by completing the modified Edinburgh Handedness Inventory (median 100, range 75-100) (VII.2.4). Primary and daily health screening and consent procedures were as laid out previously (VII.2.2).

5.4.3 Randomisation to groups

On study inclusion participants were allocated to active or sham control groups consecutively by pairs according to a randomisation chart. Double blinding, as the concealment of participants, the investigator and technical support staff to the intervention was achieved as discussed (VII.2.11.5).

5.4.4 Protocol

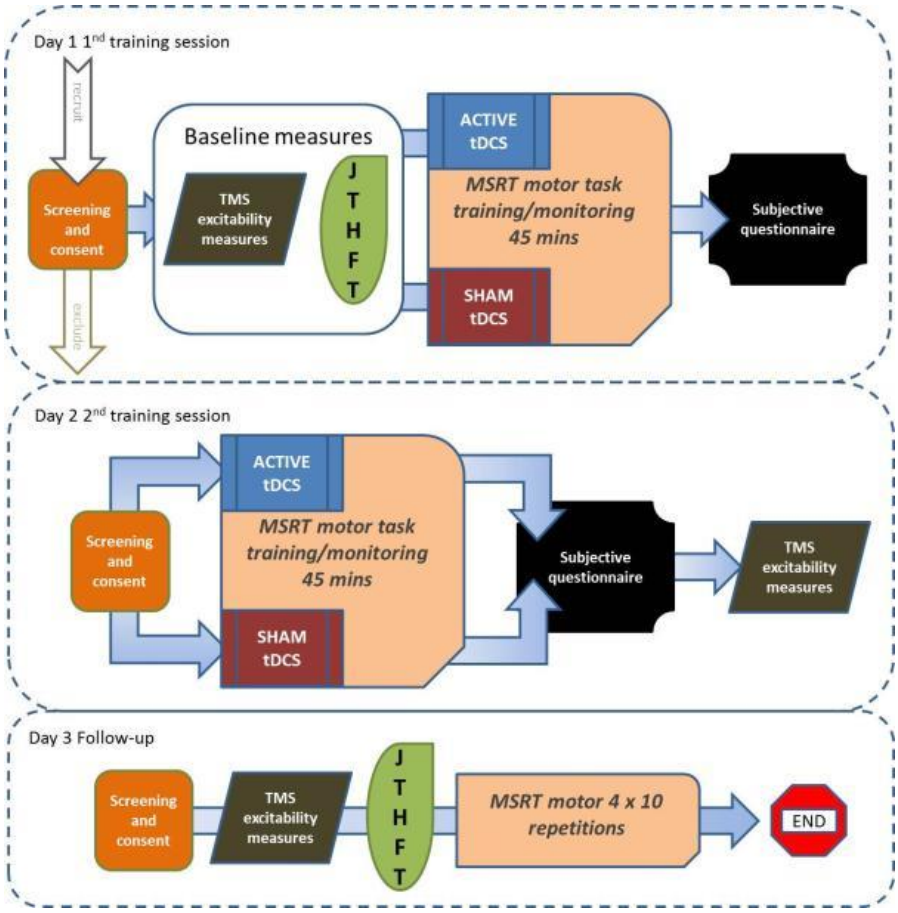


Figure 5.1: Experimental protocol.

Day 2 and Day 3 sessions were undertaken respectively 48 hours and 9 days following the Day 1 session. Volunteers were randomly assigned to ACTIVE or SHAM experimental groups on commencement and retained this assignment throughout their participation.

5.4.4.1 Overview

The double-blinded, sham-controlled experimental study extended over 2 weeks per participant (Figure 5.1). The second training session on day 2 took place 48 hours following the first session on day 1, a gap designed to reveal any intervention-dependent effects lasting beyond the key first training session and track further changes in motor skill un-confounded by mental or physical fatigue. The third, follow-up session on day 3 took place 7 days following the second session.

5.4.5 Training

Based on the findings of the preceding studies, a study protocol was produced as a reference against which all sessions were completed to time. The protocol is detailed at Appendix F.

Health screening and taking of consent took place prior to each of the 3 sessions, to assure continued fitness to take part throughout the study.

5.4.5.1.1 Day 1

Following preparations i.e. scalp measurements and attachment of surface electrodes, the gathering of baseline TMS measures from muscles abductor pollicus brevis (APB) and medial deltoid (mDelt) of the non-dominant upper limb. Two administrations of the Jebsen Taylor Hand Function Test battery (JTHFT) were then completed.

Anodal tDCS electrodes were then applied as per standardised procedure (VII.2.11). Active, or sham anodal tDCS stimulation was applied as per group allocation, for 20 minutes following baseline measurement. Training continued for 45 minutes. This consisted of repeated performances of the MSRT motor task in blocks of 10 trials, interleaved with rest breaks of around 1 minute. Participants were under no pressure to complete a specific number of trials over the duration of a session, the aim of the protocol being to avoid driving skill parameters (task completion time, or error rate) externally, which could otherwise be a potential source of bias. In any case, motor learning is thought to be an experience-dependent phenomenon which is dependent upon the period of exposure to the behavioural goal rather than the number of repetitions of a task (Eliassen, Souza and Sanes, 2003).

Following this, each participant was asked to complete a subjective questionnaire.

5.4.5.1.2 Day 2

Each volunteer underwent a further 45 minute Motor Training Period as per day 1, during which the appropriate adjunctive stimulation modality was applied for 20 minutes. Followed immediately completed a subjective questionnaire, followed by repetition of TMS-evoked measures of cortical excitability.

5.4.5.1.3 Day 3

This follow-up session was included for the gathering of lasting measures of motor skill retention, associated ability in non-trained tasks and changes in measures associated with cortical plasticity. Following screening, TMS-evoked measures to establish the extent of any

lasting changes in corticomotor connectivity were gathered from APB and mDelt. Each participant then carried out two administrations of the JTHFT. Finally, we asked participants to undergo a further 4 blocks of 10 MSRT trials.

5.4.6 Standardised intervention dosage

1.5 mA active anodal tDCS or a sham control was administered to the scalp overlying the non-dominant M1 with single blinding, hardware and procedures over the first 20 minutes of each training session as laid out (VII.2.11).

5.4.7 Task training and primary behavioural outcome measurement

The MSRT was implemented as the continuous sequential target matching task during this study (VII.2.9.4). MSRT practise was carried out in groups of 10 trials separated by short rests. Participants had minimal practise of the task sufficient to ensure that the task procedure was understood prior to the commencement of sampling on day 1.

The TPR outcome measure, derived from observations of performance in this task comprised the primary behavioural outcome measure. TPR was sampled over intervals of 30 trials from the start, at the midpoint and the final 30 trials of each session. TPR outcomes were sampled from the first 30 MSRT trials at the follow-up session.

The standardised apparatus and procedures for administering the MSRT task and deriving the TPR primary outcome measure is detailed (VII.2.9.4). The standardised task instruction to participants was as presented in Appendix B.

5.4.7.1 Instruction and verbal motivation during MSRT practise

Following demonstration of the task procedure participants were advised that spatial error was permitted and asked to work without hesitation. Participants were asked to carry out the task as quickly and accurately as possible using any preferred grasp pattern or approach, using the left arm only. This statement was repeated prior to the beginning of each successive block of 10 MSRT trials, with the terms ‘quickly’ and ‘accurately’ spoken in alternating order. During practise, mild positive reinforcement was uniformly applied in the form of short phrases such as ‘ok’, ‘good’ or ‘well done’. Negative reinforcement, criticism or any coaching of performance was strictly avoided.

5.4.8 Secondary outcome measures

5.4.8.1 Neurophysiological measures

The equipment and procedures used in the TMS-evoked measures of corticomotor excitability and short-interval cortical inhibition (SICI) are fully described (VII.2.12). The findings of a background study (VII.2.12.1) informed a time-efficient TMS measurement protocol, the precise details of which are presented (Appendix G).

Measurements of corticomotor excitability were applied at baseline, at the end of the 2nd training/stimulation session and at the beginning of the follow-up session. These were evoked by TMS and measured as motor evoked potentials (MEP) at non-dominant target muscles Abductor Pollicus Brevis (APB) and medial Deltoid (mDelt). Active state measurements were made at both these muscles with active contraction around a target value of 20% MVC EMG output relative to an MVC reference level determined at the start of each session. Resting state measurements were made at APB only.

For these procedures a hand-held Magstim single 90mm round coil antenna 9784-00 (Magsim Co., Dyfed, Wales) was used, as discussed (VII.2.12.2). The three muscle/state stimulus-response curve procedures (resting APB, active APB and active mDelt) were carried out as described (VII.2.12) in an order dictated by a pre-prepared randomisation chart.

5.4.8.2 Measure of generalizable motor function

Two repetitions of each of 5 Jebsen Taylor Hand Function Battery subtests was administered at baseline (prior to commencement of MSRT training) and follow-up prior to MSRT training as a secondary measure of generalized skill transfer. Writing and feeding subtests were not included, on the grounds that the reliability of these tests has been questioned (Stern, 1992) and secondly, that these tasks are not contextually relevant to the non-dominant hand. JTHFT aggregate scores were compiled from the average of 2 trials for each of the following sub-tests: heavy cans, light cans, checker stacking (indicators of gross upper limb function) and small object manipulation and card turning (though to depend more specifically on dextrous hand function).

5.5 Analysis

5.5.1 Behavioural data summarisation techniques

The data was analysed as absolute scores on interval scales, or converted to normalised data on ratio scales as indicated in the text.

Data in respect of completion time, error rates and TPR was **block, trial-by-trial or error-distribution** summarised to facilitate analysis of various data parameters. See Section VII.2.14 for an explanation of these 3 techniques.

5.5.2 Statistical tests

5.5.2.1 Behavioural data

Where indicated as used in the text, the test of normality used was the one-sample Kolmogorov-Smirnov test for normality, because this statistic does not rely on parameter means and variances for the population to be known: as for all statistical comparisons the level of significance was set at 5%. The measures of central tendency and variance used are the arithmetic mean and standard error of the mean (SEM), respectively. Effect sizes and 95% confidence intervals (CI) are also reported for important comparisons. Bonferroni corrections were applied for post hoc comparisons on datasets unless Levenes test proved significant across datasets, in which case Games-Howell corrections were applied.

Absolute values of the behavioural measures (TPR, JTHFT) and skill parameter of MSRT completion time were compared across groups at the baseline interval by independent t-test. This was done to confirm that the active and sham control groups were not significantly different at the outset of the study. Further tests on all outcome measures were carried out on datasets normalised to individual baseline values in order to control for the additive effect off baseline difference and group-dependent effects which could otherwise bias the analysis of data. Behavioural datasets were tested by one- or two-way way mixed-effects repeated measure analysis of variance (ANOVA). Details of variables and levels are indicated in the text. Group allocation (2 levels: SHAM or ACTIVE) was applied as the between-subjects factor in all cases. Further, post-hoc testing was applied by independent t-testing where appropriate.

We further investigated the behavioural association between independent skill parameters (task completion time, spatial error score) at each sampling interval, using Pearson's Product Moment Correlation Coefficient (PMCC). Comparison of differences in correlation across

independent conditions at key sample points were made with a paired Z test following Fisher's r-to-z transformation as a procedure for normalisation of the Pearson's r sample distributions (Sun and Wong, 2007; Jeyaratnam, 1992; Cohen, 1992).

5.5.3 Neurophysiological data

5.5.3.1 Recruitment curves/facilitated recruitment curves

Individual TMS-evoked MEP data at all intensities gathered at each measurement interval was first normalised to the baseline MT to control for inter-individual variations in motor threshold. Secondly, the average MEP value at each intensity was again normalised relative to the baseline response value to contextualise each individual's data relative to the within-subjects baseline value. This two stage normalisation procedure was carried out to effectively control for individual variations in response curve shapes. Otherwise, confounds might arise due to pre-existing inter-individual differences in the synaptic strength or distribution of intra-cortical connections in the primary M1 relative to the TMS coil. Recruitment curve datasets were tested by two-way mixed-effects ANOVA with contrasts.

5.5.3.2 Short-interval intracortical inhibition (SICI)

SICI measures were gathered in order to analyse the effect of behavioural and interventional parameters on intracortical inhibitory processes. A single round coil applied to the vertex was used to apply conditioning and test pulses at 2ms inter-stimulus interval after the method of Shimizu et al. (Shimizu *et al.*, 1999), as follows. At baseline, a TMS-evoked test stimulus at 120% RMT was conditioned by a stimulus at 80%RMT evoked 2ms beforehand. In accordance with the recommendations of Garry, these same absolute %MSO intensities were used for data-gathering at subsequent measurement intervals, as it is thought that variations in TMS intensity can independently affect estimates of this parameter (Garry and Thomson, 2009).

Ten of these conditioned test stimuli were gathered at randomised intervals as an additional state during single pulse recruitment curve protocols. Ten unconditioned stimuli as 120%RMT were also gathered and the quotient for SICI was calculated as

$$\frac{Mean\ conditioned\ MEP\ area}{Mean\ unconditioned\ MEP\ area}$$

For analysis, the SICI quotient gathered post-training at the end of the second training session and at follow-up were normalised to the within-subjects baseline quotient value.

5.5.4 Subjective tests

Standardised subjective tests of perception, in the form of numerical scale questionnaires(Appendix E) were applied at a total of 4 intervals, immediately following training sessions and at the beginning of the following session following provision of consent. See Section VII.2.5 for discussion of results.

5.6 Results

5.6.1 Behavioural measures

5.6.1.1 Baseline equality of absolute dependent measures

Group mean absolute behavioural measure descriptives for the primary outcome measure, TPR are shown in Table 5.1. Group mean scores at baseline and statistical comparisons are indicated in Figure 5.2. The independent factor of errors was not tested or analysed in depth, as the findings of Study 1 showed that high inter-individual variability, coupled with the behavioural tendency to conserve error rate, effectively confound analysis.

Independent t-testing of absolute baseline measures showed that no significant differences existed between SHAM and ACTIVE groups with respect to the primary outcome measure TPR, the skill parameter of completion time or JTHFT aggregate score.

Table 5.1: Absolute TPR values

Absolute values ± SEM for the primary outcome outcome measure TPR (Task Productivity Rate), unit of measure seconds/score. Gathered at each measurement interval (n=30 trials per participant) summarised per group (n=12 individuals).

Group		***Interval***						
		Session 1			***Session 2***			**Follow**
		Baseline	**Mid**	**End**	**Start**	**Mid**	**End**	**-up**
Sham	mean	2.010	1.730	1.536	1.588	1.518	1.535	1.645
	SEM	*0.124*	*0.092*	*0.073*	*0.075*	*0.069*	*0.071*	*0.110*
Active	mean	1.793	1.584	1.486	1.616	1.557	1.491	1.451
	SEM	*0.130*	*0.081*	*0.068*	*0.107*	*0.132*	*0.106*	*0.079*

Table 5.2: Group mean raw baseline summary statistics and between-groups statistical comparisons.

TPR skill measure (seconds/score) derived from the MSRT task skill parameters. Skill parameter of task completion time derived from MSRT practise (seconds). JTHFT measure time completion score (seconds).

Behavioural measure	*Group*	*Mean*	*SEM*	*t value*	*Df*	*p value*
TPR	SHAM	2.010	0.124	1.21	22	0.239
	ACTIVE	1.793	0.130			
MSRT task completion time	SHAM	6.260	0.218	-0.957	22	0.349
	ACTIVE	6.620	0.307			
JTHFT	SHAM	20.189	1.058	-0.421	22	0.678
	ACTIVE	20.743	0.781			

5.6.2 Analysis of learning phases

Different learning processes of motor acquisition and retention are thought to take place during ('on-line') and following ('off-line') task practise (Ghilardi *et al.*, 2009). To explore the development of group-dependent differences on TPR and the skill parameters from which the measure is derived,the study protocol was broken down into distinct phases of motor skill learning over time, and analysed accordingly.

5.6.3 TPR skill measure

Table 5.3: TPR skill outcome measure results of statistical tests.

1-way repeated measures ANOVAs for analyses of normalised TPR scores over multiple sampling intervals. Independent t-tests applied to test for effect of intervention on lasting effects of training at first sampling interval of subsequent training session/follow-up. Significant at *p≤0.05 **P≤0.001. 95% confidence intervals of the difference reported for comparisons at time points.

Phase	*Intervals*	*Effect/ comparison*	*F value/ t value*	*Df*	*P value*	*95% CI*
Protocol	7	Group	2.205	1,22	0.152	n/a
		Time	16.200	6,132	<0.001**	
		Group* time	1.798	6,132	0.104	
Session 1	3	Group	1.421	1,22	0.246	
		Time	2,44	2,44	<0.001**	
		Group* time	1.447	2,44	0.246	
Start session 2	1	t-test	-2.144	22	0.043*	-0.209, -0.003
Session 2	3	Group	3.6770	1,22	0.068	n/a
		Time	3.717	1.756, 38.635	0.032*	
		Group* time	0.955	1.756, 38.635	0.393	
Follow-up	1	t-test	-0.038	22	0.970	-0.122, 0.118

One-way rmANOVA (Table 5.3) showed that, across the 7 sampling intervals between baseline and follow-up 9 days later, the overall main effect of TIME on skill was highly significant but the main effect of GROUP was not. Likewise, the interaction of main effects did not reach significance.

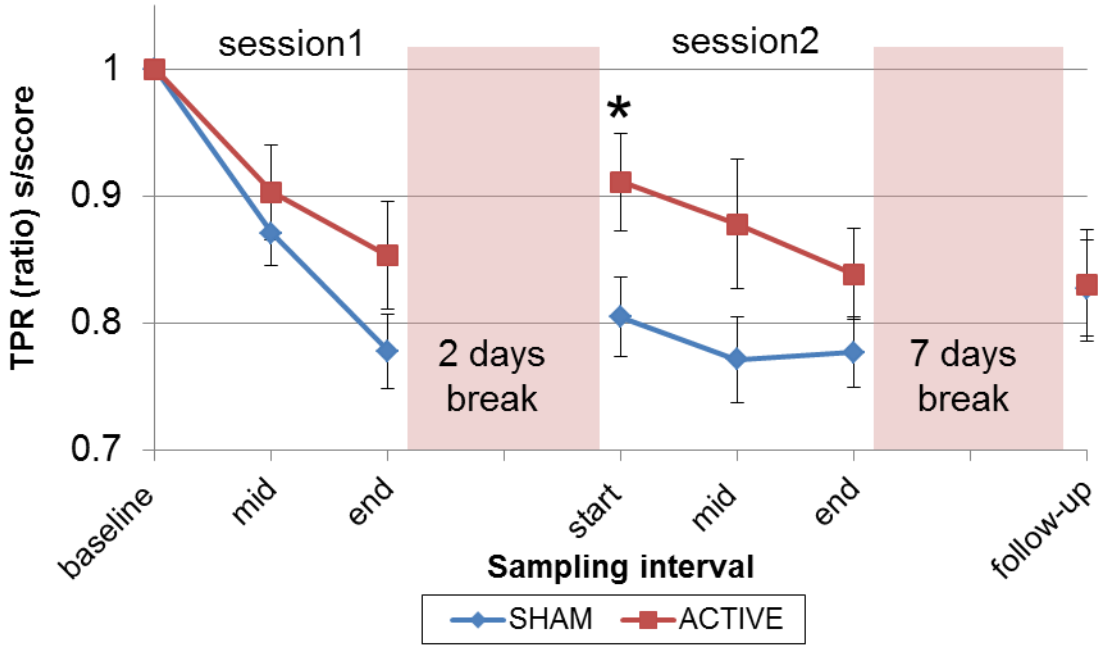


Figure 5.2: Effect of group allocation and task practise on Task Productivity Rate (TPR).

Each datapoint represents the group mean of individual TPR summary values/baseline value ±SEM. Shaded areas: 48 hour gap between sessions 1 and 2; 7 day gap between session 2 and follow-up. *significant difference between groups at start of session 2, independent t-test p≤0.05.

5.6.3.1 TPR phase analysis

The overall main effect of TIME was highly significant during the first session of practise but with no effect of GROUP or interaction between these effects (Figure 5.2).

Both groups experienced a reduction in observed motor skill between the end of session 1 and the beginning of session 2, but the ACTIVE group was subject to a greater decrement by an observed increase of approximately 6% to 91.1±3.8% of baseline value. SHAM TPR increased by approximately 3% to 80.5±3.1%. Group mean standard deviations at this interval were 0.133 for the ACTIVE group and 0.109 for the SHAM group. This combined differential rate of online skill acquisition and offline consolidation led to the normalised TPR levels reaching significant difference between groups at the first sampling interval of session 2, indicating a significant combined online and offline effect on retention which was attributable to the application of active anodal tDCS.

Over the 3 time intervals of session 2 there was an overall significant effect of practise TIME on motor skill, with a between-groups trend to significance reflecting an ongoing between-groups difference in TPR. The mean effect of task practise on SHAM performance yielded an improvement in task-dependent skill to 77.7±2.8% of baseline value by the end of session 2 compared to an ACTIVE mean value of 83.9±3.6%. Thus, between the first and last sampling intervals of session2 the between-groups difference in observed motor skill had reduced from 10.6% to 6.2%.

At the follow-up session both groups retained mean highly significant performance improvements compared to baseline (SHAM: 82.8±3.8% vs. ACTIVE: 83.0±4.4%; paired t-tests t(11)=4.55 p=0.001 and t(11)=3.88 p=0.003 respectively)such that the lasting behavioural effect of participation was a mean 17% improvement in the TPR motor skill outcome relative to baseline by both groups. Independent t-testing confirmed that at follow-up there was virtually no difference between intervention groups, indicating that there was no lasting effect of the intervention.

5.6.3.2 Effect size calculation and sample size calculation for between-groups effect on TPR at start of session 2

A significant lasting effect of anodal tDCS upon the skilled TPR outcome of MSRT performance was found at the start of session 2. Applying the known t values and degrees of freedom (Table 5.3) to Equation 2.15-1this indicated that the result at this sampling interval approached a large effect size, *r* = 0.416.

Post-hoc estimation of the sample size required to correctly reject a null hypothesis at this time interval with probability of a type II error at 20% (β = 0.2), requiring statistical power of 80% (1-β = 0.8) and level of significance 5% (α=0.05). Implementing Equation 2.15-2, with the difference between group means at (0.911 – 0.805) = 0.106 and the sham and active group standard deviations respectively 0.133 and 0.109 then from Equation 2.15-3, the independent samples

$d = \frac{0.106}{\sqrt{\frac{(0.133)^2+(0.109)^2}{2}}}$ = 0.872 (again, a large effect size according to Cohen (1992)),

And from Equation 2.15-2, n = $\frac{15.7}{(0.872)^2}$+ 1 = 21.7

Therefore a minimum sample size of 22per group would be required to meet the statistical criteria outlined. We may therefore conclude that future experimental studies investigating this phenomenon should be scaled accordingly.

5.6.4 Completion time parameter

Table 5.4:Task completion time skill parameter results of statistical tests.

1-way repeated measures ANOVAs for analyses of normalised task completion time scores over multiple sampling intervals. Independent t-tests applied to test for effect of intervention on lasting effects of training at first sampling interval of subsequent traininig session/follow-up. Significant at *p≤0.05 **P≤0.001. 95% confidence intervals of the difference reported for comparisons at time points.

Phase	*Number of Intervals*	*Effect/ comparison*	*F value/ t value*	*Df*	*P value*	*95% CI*
Protocol	7	Group	1.455	1,22	0.240	
		Time	27.073	3.916, 86.149	<0.001**	
		Group* time	1.118	3.916, 86.149	0.355	
Session 1	3	Group	0.212	1,22	0.650	
		Time	40.267	1.611, 36.441	<0.001**	
		Group* time	0.255	1.611, 36.441	0.776	
Start session 2	1	t-test	1.201	22	0.243	-0.026, 0.097
Session 2	3	Group	1.647	1,22	0.213	
		Time	16.532	1.658, 36.467	<0.001**	
		Group* time		1.658, 36.467	0.838	
Follow-up	1	t-test	1.458	22	0.159	-0.021, 0.122

5.6.4.1 Effects on completion time across entire study protocol

Completion time, normalised to individual baseline value was characterised by very highly significant time-dependent changes across the entire protocol and within each session, but group-dependent differences did not reach significance across the protocol or within phases (Table 5.4).

5.6.5 Spatial error

No significant changes or group-dependent differences were found with respect to practise TIME, GROUP allocation or the interaction between the factors of TIME and GROUP (Table 5.5).

Table 5.5:Error skill parameter results of statistical tests.

1-way repeated measures ANOVAs for analyses of normalised error scores over multiple sampling intervals. Independent -tests applied to test for effect of intervention on lasting effects of training at first sampling interval of subsequent training session/follow-up. 95% confidence intervals of the difference reported for comparisons at time points.

Phase	*Intervals*	*Effect/ comparison*	*F value/ t value*	*Df*	*P value*	*95% CI*
Protocol	7	Group	1.546	1,22	0.227	
		Time	1.162	2.511, 55.236	0.331	
		Group* time	1.202	2.511, 55.236	0.390	
Session 1	3	Group	0.735	1,22	0.400	
		Time	0.505	2,44	0.607	
		Group* time	1.682	2,44	0.198	
Start session 2	1	t-test	-1.355	22	0.189	-0.748, 0.157
Session 2	3	Group	2.118	1,22	0.160	
		Time	0.718	2,44	0.494	
		Group* time	0.492	2,44	0.615	
Follow-up	1	t-test	-0.775	22	0.447	-0.898, 0.410

5.6.5.1 Distribution of error by rail angle

To assess whether a reliable feedback condition, shown in task validation Study 1 as inferred from the distribution of error scores by angle, held in the present study, a rmANOVA was carried out on rail angle error counts summarised as a proportion of total error over each sampling interval from each participant, as per the method used in Study 1. Data from 5 intervals was analysed as follows: 30 trials at the start (baseline) and end of session 1 and for session 2, and at the follow-up session.

Table 5.6: Results of 2-way rmANOVA on proportional error distribution by angle, over time and across groups.

Data from first and last sampling intervals of sessions 1 and 2 and follow-up were included in this analysis. Because rail error distribution is expressed as a proportion of total error (value 1) for each interval and participant, independent effects of main factors of group and practise time are not relevant to the analysis.

Effect/comparison	*F value*	*Df*	*P value*
Angle	2.453	4,88	0.052
Group*angle	0.309	4,88	0.871
Time*angle	0.672	11.001, 242.018	0.764
Time*group*angle	1.135	11.001, 242.018	0.334

The main effect of rail angle approached significance (Figure 5.3) but there was no interaction with group allocation or ongoing practise. In view of the above trend, pairwise contrasts were performed for error scores across the 5 rail orientations, which showed that there were no significant pairwise differences between rail target angles. Finally, there was no practise-dependent interaction between all the main effects of practise, group allocation and error. Taken together, the analysis shows that the distribution of error across the rail array angles was statistically stable and that the scaling of error (Figure 5.3) was comparable to that seen in study 1 (Figure 3.7).

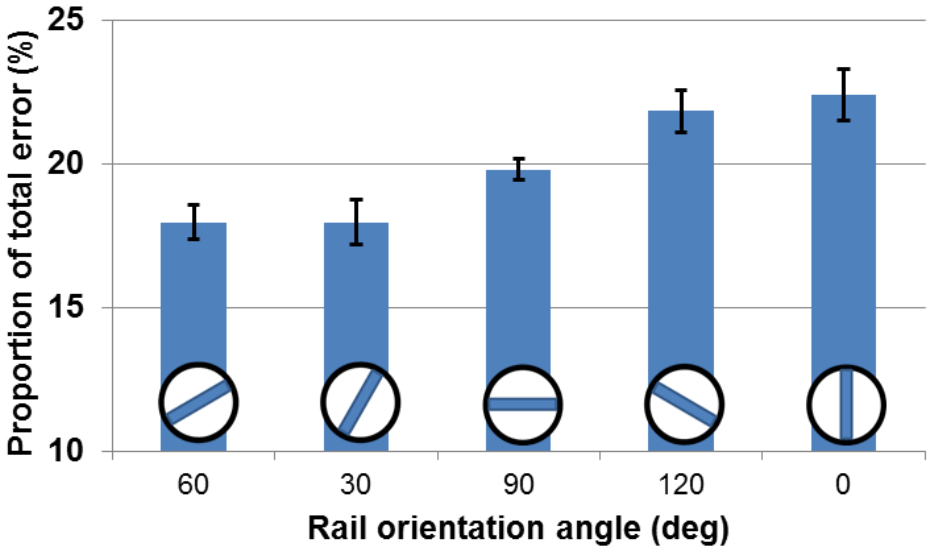


Figure 5.3: Proportional scaling of observed error distribution did not significantly vary between groups or over successive sampling intervals.

Distribution of error count per rail angle as a proportion of the total error count across all angles per interval ± SEM, collapsed across groups and 5 sampling intervals (baseline, end of session 1, start and end of session 1, follow-up).Angle graphic illustrates the respective rail orientation as seen by the participant.

5.6.6 Co-regulation of completion time and targeting errors

The series of associations between Task completion time and error (Figure 5.4) revealed a marked group-dependent difference in the development of behaviour over time. The strength of association was stable and consistently low over successive trials throughout sessions 1 and 2 for SHAM. Within the duration of the first session the trajectory of SHAM correlations was towards the positive, while that of ACTIVE was towards the negative and significantly different to that of SHAM by the end of session1 (Table 5.7), with low to moderate *negative* association between Task completion time and error over the sampling interval.

Table 5.7: Between-groups independent comparisons of Fisher's z-transformed Pearson's linear correlation r values.

The associations between task completion time and error skill parameters. All sample intervals n=30. *Z statistic ≥ critical value 1.98 for 2-tailed significance p≤0.05

session	*Sample interval*	*r SHAM*	*r ACTIVE*	*Z statistic*	*2-tailed p value*
1	baseline	0.147	0.222	-0.284	0.780
	mid	0.092	-0.110	0.741	0.460
	end	0.238	-0.329	2.149	0.032*
2	start	-0.080	0.100	-0.663	0.508
	mid	0.013	0.117	-0.386	0.348
	end	0.155	-0.04	0.722	0.470
Follow-up		0.422	0.328	0.401	0.688

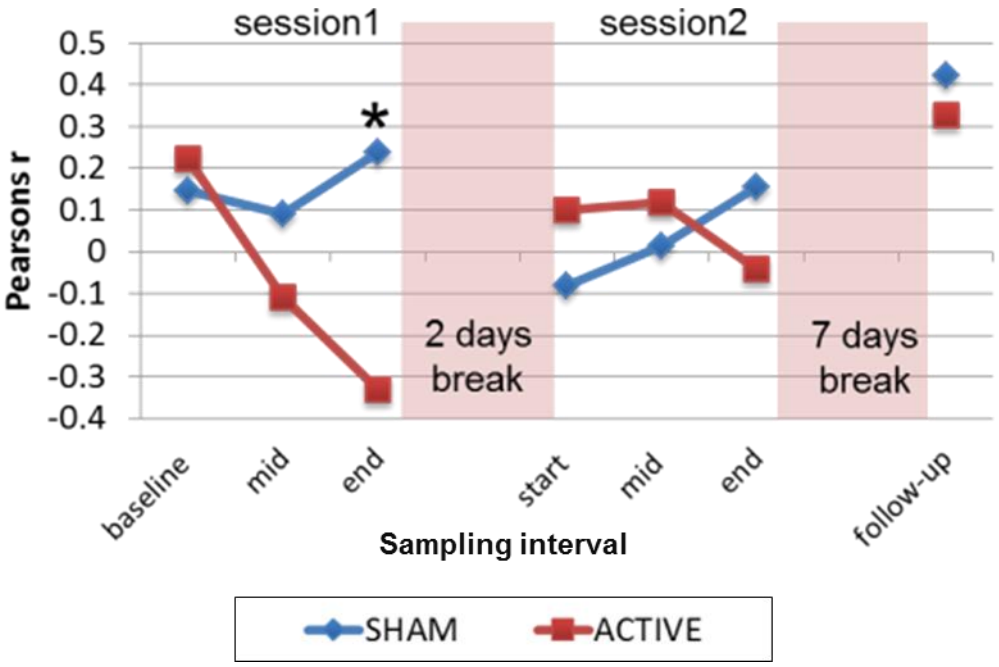


Figure 5.4: Variations in Pearsons correlations between independent variables of task completion time and spatial error.

Interval between sessions 1 and 2: 48 hours. Interval between session 2 and follow-up: 7 days. *Fishers r to z transformation comparison of correlations ≥ critical value for significant difference between independent samples $p \leq 0.05$, n=30.

5.6.7 Generalizable behavioural effects – secondary outcome measure JTHFT

The aggregate scoring of the JTHFT at the follow-up session was normalised to baseline values and subjected to independent t-testing. This procedure was also carried separately out for the aggregated scores of globally-related tasks (heavy and light cans and checker stacking) and hand-dexterity specific tasks (small objects and card turning).

Table 5.8: JTHFT secondary measure aggregate, fine and gross motor subtest comparisons.

Independent t-test results for between-groups differences in means normalised to the baseline value. Aggregate scoring of 5 JTHFT subtests and subgroup aggregates of tasks highlighting gross motor (heavy cans, light cans, checker stacking) and fine motor (small objects, card turning) functioning.

Sub-test	*t value*	*Df*	*P value*	95% CI
Total	0.366	22	0.718	-0.050, 0.072
Gross	0.139	22	0.891	-0.069, 0.079
Fine	0.476	22	0.639	-0.062, 0.100

Overall mean aggregate scorings reduced to mean 93.2±1.4%, grouped gross function scores reduced to 92.0±1.7% and fine motor scores to 94.7±1.0% of the baseline scores. The results of independent t-test comparisons by group of measurements taken at the follow-up session were all non-significant (Table 5.8) suggesting that group allocation had no significant lasting effect on generalizable aspects of motor function, within the previously-discussed limitations of this outcome measure in the healthy population (VII.1.8.1).

5.6.8 Neurophysiological outcome measures

5.6.8.1 Motor thresholds

5.6.8.1.1 Baseline equality of measures

Separate independent t-tests of absolute motor threshold (MT) values showed that, while small differences existed between the group mean MT central tendencies of respective muscles and states, these were not significantly different (Table 5.9).

Table 5.9: Group mean raw value motor thresholds baseline summary statistics and statistical comparisons.

Motor threshold evoked at baseline measurement interval from resting state APB, active state APB and mDelt. Unit of measure % maximum stimulator output (%MSO).

State/muscle	*Group*	*Mean*	*SEM*	*t value*	*Df*	*P value*
Resting APB	SHAM	50.50	1.584	0.858	22	0.400
	ACTIVE	48.25	2.089			
Active APB	SHAM	36.75	1.661	0.596	22	0.557
	ACTIVE	35.42	1.500			
Active mDelt	SHAM	41.42	1.751	-0.095	22	0.925
	ACTIVE	41.67	1.959			

5.6.8.1.2 Motor thresholds

Separate one-way rmANOVAs with contrasts were carried out on each muscle/state over 3 time intervals.

Table 5.10: Motor thresholds, separate 1-way rmANOVA comparisons for each muscle state.

Repeated measures over 3 time intervals. Significant at **p≤0.01

State/muscle	Effect/ comparison	F value	Df	P value
Resting APB	Group	1.246	1,22	0.276
	Time	0.766	2,44	0.471
	Group*time	0.499	2,44	0.487
Active APB	Group	0.411	1,22	0.528
	Time	2.870	2,44	0.067
	Group*time	0.298	2,44	0.744
Active mDelt	Group	0.121	1,22	0.731
	Time	5.461	2,44	0.008**
	Group*time	1.194	2,44	0.313

This procedure showed that no significant variations in rAPB resting motor threshold (RMT) occurred over TIME, between GROUPs, or due to an interaction between the main effects. The mean intensity remained largely stable at end of session 2 (48.708±1.181%MSO) and follow-up (48.958±1.173%) against the mean baseline value of 49.375±1.311%MSO

Analysis for aAPB showed an effect for TIME approaching significance, with MTs reduced from 36.083±1.119 to 34.875±1.113 and 34.625±1.207%MSO at the end of the second session and follow-up intervals respectively, but with no GROUP effect or interaction between effects.

The main effect of TIME upon amDelt AMT was highly significant but with no significant GROUP effect or interaction of effects. Contrasts showed that, compared to the baseline threshold stimulator intensity of 41.542±1.314%MSO, by the end of training the mean AMT was reduced to 39.917±1.325%MSO, $F(1,22)=7.986$ $p=0.010$, and further reduced to 39.542±1.352%MSO, $F(1,22)=10.896$ $p=0.003$ at the follow-up session a week later.

5.6.8.2 Recruitment and facilitated recruitment curve results

Table 5.11: Stimulus-response curves, results of separate 2-way rmANOVAs for each muscle/state.

Repeated measures over 3 time intervals. Significant at *p≤0.05 **p≤0.01

State/muscle	Effect/ comparison	F value	Df	P value
Resting APB	Group	3.018	1,22	0.096
	Time	0.581	2,44	0.564
	Time*group	0.919	2,44	0.406
	Intensity	2.079	4.039, 88.852	0.090
	Group*intensity	6.082	4.039, 88.852	0.038*
	Time*intensity	0.892	4.344, 95.566	0.479
	Group*intensity*time	1.194	4.344, 95.566	0.318
Active APB	Group	1.275	1,22	0.271
	Time	5.988	2,44	0.005**
	Time*group	0.806	2,44	0.453
	Intensity	2.556	2.796, 61.591	0.067
	Group*intensity	1.285	2.796, 61.516	0.287
	Time*intensity	1.711	5.578, 122.720	0.129
	Group*intensity*time	1.031	5.578, 122.720	0.406
Active mDelt	Group	0.410	1,22	0.529
	Time	1.731	2,44	0.189
	Time*group	0.847	2,44	0.435
	Intensity	1.646	3.486, 76.684	0.179
	Group*intensity	2.649	3.486, 76.684	0.047*
	Time*intensity	1.218	8.048, 117.057	0.291
	Group*intensity*time	1.976	8.048, 117.057	0.051

5.6.8.2.1 Resting APB recruitment curves

In general, sustained mean increases in MEP area were noted at all TMS intensities by SHAM relative to within-groups baseline values. ACTIVE responses hardly varied relative to baseline (Figure 5.5A).

Against normalised baseline intensities there was no significant net main effect of TIME but there was a trend to significance for the main effects of INTENSITY and GROUP and the interaction of INTENSITY*GROUP reached significance. Furthermore, contrasts showed that the significant INTENSITY*GROUP variation in response compared to baseline was specific to 110% of RMT $F(1,22)=6.082$ $p=0.022$ (Figure 5.5A), indicating that this intensity-specific relationship was stable across both post-intervention measurement intervals following baseline measurement. In summary, the significant facilitatory change seen in SHAM MEP responses over the sessions following practise appear due to the group allocation and persist for 7 days following training.

5.6.8.2.2 Active APB facilitated recruitment curves

The TMS-evoked MEP area responses of both groups became elevated at all intensities over the period of study participation (Figure 5.5B).Although visualisation of the data suggests sustained between-groups variations at moderate intensities, ANOVA revealed a highly significant effect of TIME (Table 5.11) with a trend to significance for INTENSITY but no main effect of GROUP or interactions between the main factors.

5.6.8.2.3 Active mDelt facilitated recruitment curves

Visualisation of the data indicated that sustained increases in MEP area occurred in this muscle in both groups (Figure 5.5C). For the SHAM group, slightly greater mean increases were seen at high TMS intensities, increased at follow-up, with no changes at low intensities. Conversely, sustained increases in ACTIVE group MEP areas were seen at all TMS intensities and to a slightly greater extent at low intensities.

There was no significant main effect of TIME, INTENSITY or GROUP (Table 5.11). There were, however, significant interactions of INTENSITY*GROUP shown by contrasts to be specific to 110% of AMT ($F(1,22)=4.907$ $p=0.037$) and a close trend to significance for INTENSITY*GROUP*TIME at 110% of AMT, which contrasts reported to be significant at the post-training stimulation interval ($F(1,22)=6.051$ $p=0.022$).

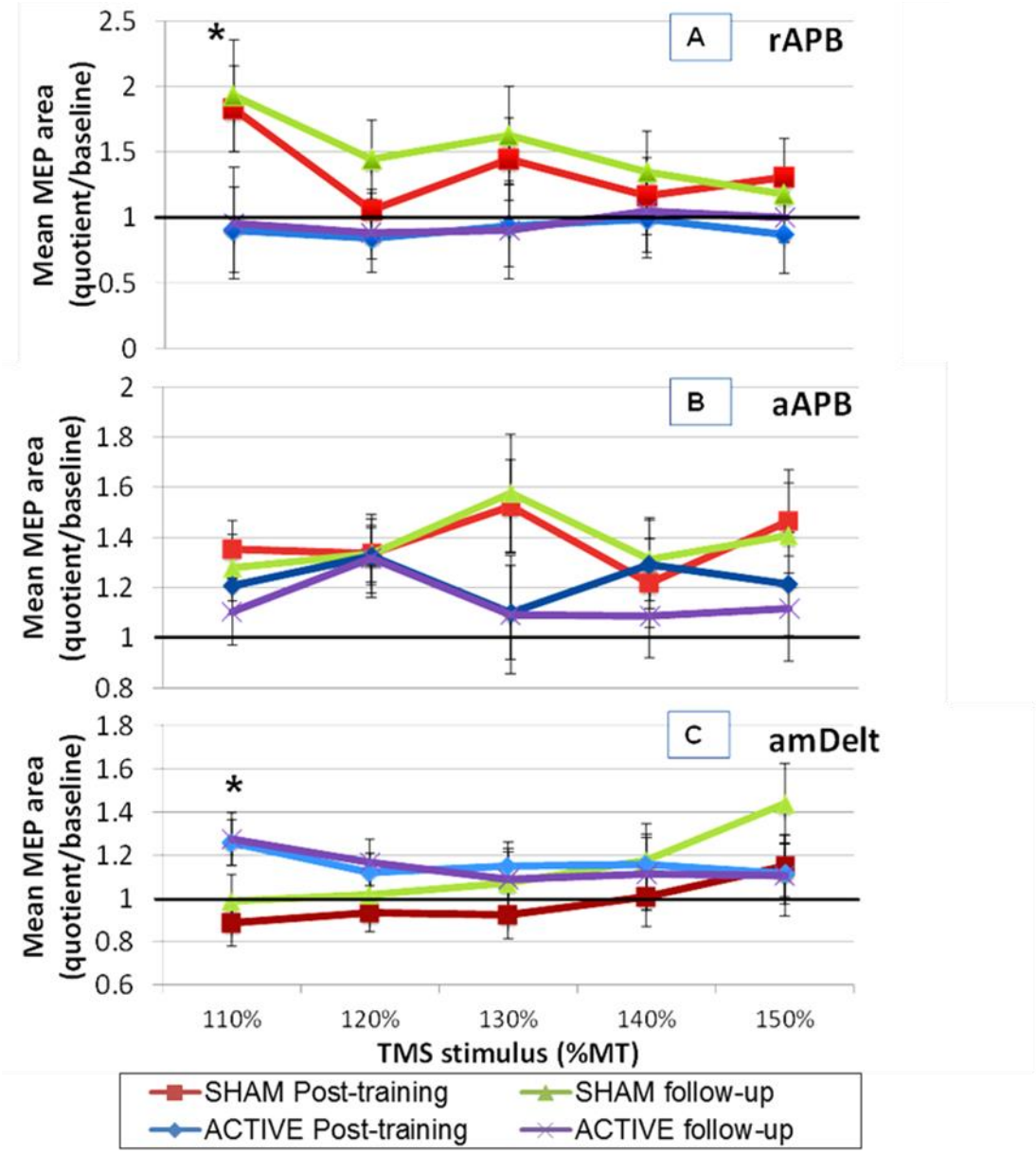


Figure 5.5:Significant group-dependent effect of intervention on TMS stimulus/response ratios at 110% of MT compared to baseline, expressed from resting distal (APB) and active proximal (mDelt) target muscles.

A) relative to respective normalised baseline stimulus values for APB at rest (rAPB). (B) active APB (aAPB) and medial Deltoid (amDelt) activated to 20% of maximum EMG respectively. *Post-training* measurement interval: immediately following the 2nd training/stimulation session. *Follow-up* measurement interval: 7 days thereafter. *significant GROUP*INTENSITY main effect interactions with significant post-hoc between-groups differences at 110% of MT across time intervals after baseline $p<0.05$. Note differences in ordinate scaling.

5.6.9 Short-Interval Intracortical Inhibition (SICI) at resting APB

Analysis of the 2ms SICI quotients by one-way rmANOVA showed that TIME was a significant factor in the variation of SICI (Table 5.12). Contrasts revealed a highly significant elevation of the quotient and thus a reduction of inhibition $F(1,22)=12.668$ $p=0.002$ at the post-training interval (SHAM 1.465±0.187; ACTIVE 1.479±0.187) relative to baseline which was not significant at follow-up (SHAM 1.174±0.249; ACTIVE 1.517±0.250) $F(1,22)=3.838$ $p=0.063$. However, there was not a significant GROUP effect nor was there a significant interaction between these main effects.

Table 5.12: Time and group dependent effects on SICI evoked from resting APB.

Results of 1-way rmANOVA, effect of practise and intervention on short-term intracortical inhibition at 2ms .

Effect/ interaction	F value	Df	P value
Group	0.495	1,22	0.489
Time	4.384	2,44	0.018*
Group*time	0.690	2,44	0.507

5.7 Discussion

5.7.1 Main findings

There was a statistically significant lasting effect on spatial motor skill specific to the first sampling period following 48 hours rest, in favour of a superior improvement in skill by the SHAM group. However, the criteria of the primary research question refer to lasting effects at the 7 daysfollow-up interval. No such difference existed between group TPR scores at that interval. Therefore the alternate hypothesis in respect of the primary research question was rejected.

The criterion for testing the secondary research question was defined in relation to data gathered prior to task practise at the follow-up session, 7 days following the end of the training/intervention protocol. A mean statistically significant relative enhancement of TMS-evoked MEP areas was found at 110% of motor threshold in resting APB in the SHAM group, which was stable across both the post-intervention measurement interval and at follow-up. There was not a significant between-groups difference specific to the follow-up session. Therefore, in respect of the secondary research question, there was not sufficiently strong evidence to reject the null hypothesis.

5.7.2 Comparisons with previous behavioural findings

These behavioural findings appear superficially to run counter to those previous studies which report the short-term benefits of anodal tDCS on performance in complex motor tasks in healthy individuals (Sohn, Kim and Song, 2012; Hummel *et al.*, 2010; Boggio *et al.*, 2006a) and patient groups (Bolognini *et al.*, 2011; Kim *et al.*, 2009; Hummel *et al.*, 2005). The current results indicated that following training and 48 hours rest, the group receiving active intervention achieved a skill level significantly worse than the sham group. But, while the stimulation parameters of the anodal tDCS intervention used in the current project in these studies are very similar to those used in previous studies, the design of these studies is different to ours in important respects.

The novel TPR measure captures the univariate outcome of skilled performance in both temporal and spatial dimensions, whereas the common metric in clinical studies is the dimension of time. But, as previously discussed (VII.1.8.1), for a number of reasons the sole use of the temporal parameter as a metric of skill may be problematic. Fundamentally, the nature of task completion time as an outcome measure is that, as found in Study 1 movement

rates can be subject to bias by behavioural influences, and does not include information relating to spatial variability or error, either in relation to kinematics or the end-points of the behavioural goal. The protocols of previous studies typically involved pre-training in a validated task to a stable state, followed by application of anodal tDCS and then re-measuring following the stimulation intervention to establish changes in motor function (Tecchio *et al.*, 2010; Hummel *et al.*, 2005). Secondly, and more importantly, with respect to the interpretation of results, the properties of the TPR skill measure are fundamentally different to the outcome measures commonly applied in previous studies (VII.1.5).

Further highlighting the potential limitations in relation to the interpretation of previous studies, anodal tDCS has also been shown to have a lasting positive effect on reaction times in SRTT-based paradigms (Kang and Paik, 2011; Nitsche *et al.*, 2003). A further study looked at the effect of anodal tDCS on the short-term enhancement of task consolidation i.e. continued improvements in a pre-learned SRTT-like task following the end of training (Tecchio *et al.*, 2010). The significantly reduced completion time in the trained SRTT task sequence was attributed to strengthening of trained cortical networks (Tecchio *et al.*, 2010).

A potential confounding factor in the interpretation of such studies is that the metric from SRTTs is response latency, from which changes in the strength of implicit motor memory could be inferred (Ghilardi *et al.*, 2009). However the same result could be at least partially attributed to an enhancement of motor force/time activation due to the intervention rather than a strengthening of the motor memory per se as, even during procedural learning of the SRTT motor sequence, the major part of the skill improvement is thought to be due to reductions in movement time (Moisello *et al.*, 2009). Likewise, application of anodal tDCS concurrently during explicit learning of an SRTT-type task led to an ongoing enhancement of reaction times compared to sham or cathodal tDCS conditions, while the application of anodal tDCS prior to the learning period had a negative, slowing effect on reaction times(Stagg *et al.*, 2011). The authors attribute this disassociation of effects to a homeostatic mechanism acting upon motor learning at the cortical level based upon the order of stimulation and training. But the finding that, starting measurements following the 10 minute stimulation period resulted in a relative diminution of response time results relative to the other experimental conditions over the 15 minute period of the protocol, suggesting that response latency was tied to the state of excitability of the M1 region(Stagg *et al.*, 2011). Accordingly, it has been shown that reducing the excitability of M1 using repetitive TMS reduced the capacity of individuals to produce rapid movements (Jäncke *et al.*, 2004).

A further, novel task paradigm applied a range of guided movement rates dependent upon the mechanical activation of a single degree-of-motion mechanical pinch force interface, with the environment of the virtual task featuring a positive force field. Improvements in motor skill were inferred from shifts in the log-linear gradient of the speed/accuracy trade-off during repetitions of a standardised sequential task, demonstrating significant enhancements of the speed/accuracy tradeoff over measurement intervals extending up to 3 months from the intervention period (Reis *et al.*, 2009). But in deriving the skill measure several potential flaws were introduced, as previously discussed in some depth (VII.1.8.1).

Galea and colleagues found in a cross-over study that adjunctive anodal tDCS increased the magnitude and duration of practise-dependent movements in the trained direction subsequently as evoked by high-intensity TMS over the short term (<50 minutes) and which was associated with increases in cortical excitability, again suggesting that anodal tDCS enhanced the encoding of motor memories (Galea and Celnik, 2009). However an alternative explanation is equally valid, that motor force output in the practised direction could be enhanced by the intervention to produce the behavioural gain.

In further support of this idea, a number of studies have established the effects of anodal tDCS on short-term enhancement of motor strength (Tanaka *et al.*, 2011; Hummel *et al.*, 2006) and endurance (Cogiamanian *et al.*, 2007; Hummel *et al.*, 2006; Hummel *et al.*, 2006).There are further findings that anodal tDCS may have the capacity to shorten the time-course of adaption but lengthen the period of de-adaption to a resistive artificial force-field(Hunter *et al.*, 2009) and increase the magnitude of learning-dependent change in simple joint kinematics through a combination of motor practise and adjunctive stimulation (Galea and Celnik, 2009). In summary, there is evidence that anodal tDCS may have a primary effect on force output to support movement rate, rather than some enhancement effect on motor memory formation.

As an overarching observation, because the movement rate of the end effector depends upon angular acceleration (force/time) a general observation in respect of studies to date is that the behaviours under-pinning positive outcomes in studies utilising these outcome measures could be actually be delivered by enhanced muscle activation alone. This notion cannot be discounted unless the effect upon the variability of the behavioural end-point(s) is also considered. These examples highlight the obvious point, that the interpretation of physical states is limited dependent upon the sensitivity and specificity of the outcome measure implemented. The current TPR skill measure captures the interaction of two interacting parameters in a univariate measure of reliability in relation to a standardised behavioural goal

and thereby has the capacity to convey additional information about the consequence of experience and interventions on the skill outcome.

5.7.3 Motor thresholds

MT values, established visually from MEP amplitude responses, and their associated TMS stimulus intensities were established according to generally accepted criteria (VII.2.12) at the baseline measurement interval and these reference threshold intensities and derived intensity series' were also applied at the subsequent two measurement intervals. We took this approach acting upon the concern that variations in TMS test stimulus based upon changes in MT over successive measurement intervals could confound measurements of SICI (Garry and Thomson, 2009).This approach was also taken in order to control for the subjective element of motor threshold determination. That is, determination of MTs was carried out based upon responses from a limited number of TMS-evoked responses, but these vary stochastically about a mean value and so precise MTs cannot be determined (Thickbroom, Byrnes and Mastaglia, 1999).

Highly significant reductions in the AMT from active mDelt were found at both measurement interval compared to baseline, along with a trend to significantly reduced AMT of APB. Neither of these time-dependent variations was close to significance between the groups. MTs are considered to reflect the net excitability of the lowest-threshold motor neuron populations (Hess, Mills and Murray, 1987) hence could represent a time-dependent increase excitability of synapses at the dendrites of descending pyramidal neurons in the primary M1 due to motor practise. However the effect was seen under activation only and so might result from an enhanced response to the same descending stimulus from other sites in the corticomotor pathway (Kidgell *et al.*, 2010). It cannot be discounted that such changes in corticomotor excitability could similarly alter the responses evoked during the gathering of SRcs. But any non-specific variations in excitability, which might apply linear gain across the stimulus range above threshold, were controlled for in the normalisation procedures for SRcs outlined below.

5.7.4 Persisting changes in corticomotor excitability

TMS-evoked SRcs are thought to be reliable means of characterising corticomotor excitability over sampling intervals spaced over hours (Devanne, Lavoie and Capaday, 1997) and days (Carroll, Riek and Carson, 2001; Malcolm *et al.*, 2006). Successively higher stimulus intensities are thought to elicit responses from less excitable neuron populations, or those further from

the stimulation locus (Hallett, 2000). Because we utilised a large, non-focal coil for these measurements it is reasoned more likely that the current results principally reflect net changes in excitability of all projections to the target muscles. But the interpretation of time-dependent changes in these results must take account that changes in net excitability along the entire corticomotor pathway could be responsible, including the corticospinal tract, spinal neurons, neuromuscular junctions and/or muscle fibres (Ziemann *et al.*, 1996).

Testing M1 corticomotor excitability of the APB thumb muscle in the resting state we found significant between-groups differences at low MEP intensities above the resting motor threshold, at the completion of training and at follow-up a week later. The mean value of MEP area responses was almost doubled at 110% of motor threshold in the sham group relative to baseline, suggesting that those who did *not* receive active stimulation benefitted specifically in respect of enhanced suprathreshold responsiveness. This effect was found immediately following training and also at a week following training, suggesting that these results reflected, in the main, consolidated states of motor memory.

In humans, improvement in the operation of motor skills correlates with progressive M1 reorganisation (Karni *et al.*, 1998) and increases in resting state M1 recruitment curve excitability which are not found following non-skilled training (Perez *et al.*, 2004). Short-term enhancement of performance in simple motor tasks has also been related to focal facilitation of MEP amplitudes (Muellbacher *et al.*, 2001). Increased resting state MEP amplitudes have also been related to expert manual ability in sportspersons (Pearce *et al.*, 2000). Increases in cortical excitability of upper limb muscles involved in repeated skills training, resulting in progressive enhancements to MEP responses at and above threshold have been found in the resting state at cortical representations (Jensen, Marstrand and Nielsen, 2005a). But facilitated responses from muscles in the active state may confer different information to those evoked in the resting state. Experience-dependent changes which have been found at the cortical level (Monfils, Plautz and Kleim, 2005; McKay *et al.*, 2002; Pearce *et al.*, 2000) might also occur downstream in the corticomotor hierarchy, for example via changes in motor unit activation. TMS-evoked measures applied using the current methods represent the net result of excitability changes which could occur at any point between the stimulation site at M1 and the production of the electromyogram at the target muscle. The synchronous activation of motor units is also thought to be important in training-induced changes in muscle output in both hand and proximal muscles (Fling, Christie and Kamen, 2009) implying that changes in the

corticomotor organisation of activation circuitry could take place at several corticomotor levels simultaneously (Carroll *et al.*, 2011; Duchateau, Semmler and Enoka, 2006).

Accordingly, the group-specific augmentation of facilitated MEP areas in favour of the group receiving active stimulation could be partially due to conditioning factors resulting from the power requirements of the higher movement-rate movement strategy in this group. In general, EMG activity is increased in the early stages of strength training (Moritani and deVries, 1979) and decreased following several weeks of limb unloading (Deschenes *et al.*, 2002). However, other studies implementing weeks of simple strength training found no significant change in corticomotor parameters evoked from the active muscle (Jensen, Marstrand and Nielsen, 2005a). But the patterns of experience-dependent plasticity in cortical and spinal circuits seem to vary dependent upon the strategy utilised to achieve the behavioural goal of the task, with the demands of skill and strength relating to the degrees of plasticity at the cortical level and spinal level respectively (Adkins *et al.*, 2006) emphasising the innate flexibility and redundancy within sensorimotor systems in the solution of diverse behavioural and environmental challenges.

Over the time-course of the study, the effect of time was significant on the facilitated recruitment curve of the active APB muscle, indicating task dependent increases in connectivity in the active thenar muscle which is important in pinch grasping which was common to both groups. That is, indicators of non-group specific increases in facilitated cortical activation were seen over time in the distal thenar muscle which was equally active in both groups during grasping and placement. This result is consistent with that of recent studies looking at the effect of 4 weeks strength training on corticospinal strength to active target hand muscles, which observed significant increases in force production but with no significant effect on MEP amplitudes (Kidgell and Pearce, 2010). It could be inferred that enhancement of suprathreshold MEP responses in the active hand muscle may simply reflect increases in corticomotor drive related to activity rather than skills learning.

To our knowledge the current study is the first to have assessed time-dependent changes in corticomotor excitability due to anodal tDCS. Persisting significant increases in suprathreshold corticomotor excitability compared to baseline were observed in mDelt of the active group. A highly significant, non-group dependent reduction in motor thresholds was also found. Each single trial of the MSRT included multiple abduction repetitions of the left-side gleno-humeral joint of the shoulder from rest, over up to 150 trials of practise in a single session. Because the physical dimensions of the MSRT task are fixed, faster mean movement rates between fixed

points must have been underpinned by greater repetitive angular accelerations of the upper limb load from rest. Power production in proximal upper limb muscles has been shown to be maximal under low loading conditions from rest (Newton *et al.*, 1997). High-velocity ballistic exercises in the low-loading state are a highly effective means of short-term strength training (Cronin, McNair and Marshall, 2001) and intent, whereby voluntary drive appears to be as important a component as the muscle contraction rate in determining the behavioural and physiological effects of high-velocity training (Behm and Sale, 1993), which suggests that some experience-dependent refinement of the movement takes place over time. There are recent findings that, converse to the findings in respect of non-skilled training in the hand muscle (Kidgell and Pearce, 2010), MEP amplitudes at motor threshold and all stimulation intensities up to saturation are significantly increased concurrent with short term strength training of proximal upper limb muscles over repeated sessions, suggestive of a neurophysiological adaption dependent upon the conditioning behaviour (Kidgell *et al.*, 2010).

The ensemble activation of proximal and distal muscles in reaching and hand rotation to targets, in an activity similar to the MSRT sequence of movements, seems to rely on the activity of a common population of motor cortical neurons in M1 (Wang *et al.*, 2010; Graziano, Taylor and Moore, 2002). Error-based corrections in response to systematic environmental perturbations, which may be internal or external, are involved in the development of persisting, use-dependent movement solutions which are both implicit and persistent (Diedrichsen *et al.*, 2010). Studies in primates demonstrate the exponential reduction in the spatial variability of movement trajectories with practise as the main determinant factor in skill improvement in aimed tasks (Georgopoulos, Kalaska and Massey, 1981). This finding has recently been repeated in humans, and thought to be driven mainly by changes in motor and sensory representations that increase the neural signal-to-noise ratio, as distinct from the model-based mechanisms in cerebellum that quickly reduce systematic sources of error (Shmuelof, Krakauer and Mazzoni, 2012).

In summary, the significant persisting group-dependent increase in the cortical projections to the resting APB muscle suggest that learning took place relating to improved target matching in the SHAM group. The significant increases in suprathreshold MEP responses compared to baseline evoked from the active APB of both groups may reflect common levels of activity, while the group-dependent increase in MEP responses gathered from the active mDelt at low intensity is indicative of activity-dependent corticomotor conditioning associated with greater proximal muscle activation to attain the behavioural goal.

5.7.5 Indicators of training-induced cortical plasticity

Short-interval intracortical inhibition (SICI) conditioning and test responses were gathered at 2ms paired pulse interstimulus interval from the resting thumb muscle APB during gathering of the SRc for this muscle state. We found that both groups experienced highly significant reductions in SICI between baseline measurement and the measurement immediately following the 2nd training session. However there was no group-specific effect.

SICI at 2ms is thought to reflect the net state of inhibition in intracortical circuits in M1, depending upon synaptic interactions likely to be mediated by GABAergic inhibition (Roshan, Paradiso and Chen, 2003). Reductions in SICI have been related specifically to the learning of a motor skill involving the target muscle (Smyth, Summers and Garry, 2010), which could represent a training-induced adaptation of corticospinal modulation related to enhanced dexterity (Rosenkranz *et al.*, 2005). Learning in the motor cortex is thought to depend upon synaptic plasticity (Baraduc *et al.*, 2004; Muellbacher *et al.*, 2001). A strong determinant of synaptic strength which remodels neural network activity in learning is use-dependence (Raineteau and Schwab, 2001).Post-synaptically induced NMDA-dependent, $GABA_A$-mediated long-term potentiation (LTP) is a key mechanism in formation of experience-dependent synaptic plastic (Rebola, Srikumar and Mulle, 2010). But focal application of anodal tDCS at rest can also give rise to increases in $GABA_A$ modulation (Stagg, Bachtiar and Johansen-Berg, 2011) and energy expenditure (Binkofski *et al.*, 2011) within M1, which might underlie behavioural gains in time-sensitive practical outcome measures such as the JTHFT or serial reaction time task (SRTT) as a secondary effect of relatively prolonged cortical activation (Stagg *et al.*, 2009).

Thus, natural and synthetic processes driving motor activity and learning may interact at the synaptic level, with the material difference being that the natural process is task-specific while the synthetic process is not. It is possible that, while SICI decreases in the resting thumb muscle in the SHAM group were directly due to task practise, application of anodal tDCS acted to reduce cortical inhibition in a non-specific fashion (and without the associated skill increase) resulting in the matching of SICI quotients at the measurement interval immediately following the second session, but via differing mechanisms. Perhaps anodal tDCS could interfere in some fashion with the laying down of motor memory in M1. In fact, SICI is reduced in those suffering dystonia of the hand, indicating that extant states of generalised cortical disinhibition in M1 might affect plasticity processes associated with motor learning (Quartarone *et al.*, 2005).

It has been proposed that regulatory metaplastic mechanisms operate in order to prevent LTP-driven destabilisation of the cortical networks involved in prior learning activity (Abbott and Nelson, 2000). Thus, metaplastic effects are timing-dependent (Bienenstock, Cooper and Munro, 1982). This mechanism has been demonstrated experimentally whereby subsequent cortical stimulation with repetitive TMS can reverse the effects on cortical excitability usually found after anodal and cathodal tDCS (Siebner *et al.*, 2004; Lang *et al.*, 2004). Indeed, application of anodal tDCS prior to motor task training might interfere with subsequent learning (Stagg *et al.*, 2011; Kuo *et al.*, 2008), or perhaps vice versa. But because we applied anodal tDCS concurrently during MSRT practise from the naïve state, we controlled for the possibility that order effects might interfere with acquisition of skill. Furthermore, in sampling directly from motor practise we also observed that the mean group-dependent differences in learning were not only practise-dependent but also consistent. Thus, while anodal tDCS might interact directly with processes involved in the laying down of motor memory we have no evidence that metaplastic mechanisms operated in the present study.

5.7.6 The chronology of intervention-dependent effects on behavioural and neurophysiological outcomes

The current findings concur with those from Study 2, which suggested that the lasting effects of anodal tDCS might be unrelated to the enhancement of motor skill. In fact, we found that the intervention of anodal tDCS caused a relatively poorer retention of spatial motor skill which was chronologically associated with an early disruption of motor control. The effect of group allocation over task practise during the first session, followed by 48 hours rest, resulted in significantly better skilled performance in the healthy subjects receiving SHAM stimulation at the start of the 2nd session (Figure 5.2). By the follow-up session observed motor skill was essentially the same across both groups. Likewise, there was no lasting effect of the intervention over the 9-day period of the study with respect to the secondary measure of manual dexterity, the JTHFT.

The time-dependent, systematic state of co-regulation were analysed over successive sampling intervals, and found that at baseline and follow-up sessions both intervention groups implemented similar relationships between task completion time and error rate. SHAM mean group behaviour was characterised by a consistent weak positive association between completion time and error rate over the entire training period. Conversely, over the mid and final 30 MSRT trials of Session 1 a weak negative association was present between the skill

parameters in the behaviour of the ACTIVE group. The difference between the group mean co-regulation behaviours was found to be significant over the final sampling interval of Session 1, which was interpreted as a significant disruption of behaviour from the norm control condition.

The implication in relation to the online effect on motor behaviour is that a significant group-dependent disruption of co-regulation between motor enactment and observation of spatial error may have contributed to the significant between-groups difference in motor performance. This could have been related to the effect of the active intervention upon co-regulation of the skill parameters towards the end of Session 1. The addition implication of the results in relation to offline motor *learning* is that there might have been a lasting detrimental effect on performance by the ACTIVE group at the first sampling interval of the second practise session 48 hours later. The net combined online and offline effect of active anodal stimulation upon skill learning from the naïve state impaired subsequent performance of the motor skill during the first sampling interval at Session 2, resulting in a significant relative impairment in the TPR outcome.

In the interests of practicality we did not measure relative changes in corticomotor excitability over the duration of individual sessions. Corticomotor excitability measures collected immediately following Session 2 training probably represent cumulative effects which are at least partially long-term in nature, by virtue of the plasticity of M1 cortical representations which are thought to underlie lasting motor skill improvements. We can be more confident that the group mean measures gathered at the follow-up session prior to training capture systematic, lasting effects which are sufficiently stable to be detected at 7 days post-training. Thus, the TMS-evoked measures in the current study in the main represent the outcome of the history of interaction between the non-focal intervention and motor practise i.e. systematic effects upon motor memory. Significant group-specific TMS response enhancements compared to baseline were found following training and persisted at follow-up in the resting APB representation in favour of the SHAM group, while again persistently increased excitability was evoked at the active mDelt in favour of the ACTIVE group.

In summary, ACTIVE application of anodal tDCS to M1 was found to be associated with lasting plasticity in brain areas projecting to the shoulder muscle, following observation of a significant short-lasting disruptive effect on the co-regulation of skill parameters and subsequently impaired performance of spatial motor skill. Conversely, more rapid skill learning and superior retention under the SHAM condition, was followed by superior lasting cortical

plasticity in the hand muscle representation. Taken together, this evidence suggests a lasting *disassociation of plasticity* associated with the short term, group-specific effects upon behaviour. Both of the effects on corticomotor excitability were seen at low applied TMS levels indicating that, depending upon the modality of brain stimulation significantly different responses to threshold activation emerged at muscles involved in distinct elements of the sequential prehension task.

5.7.7 Effects of anodal tDCS on motor control and learning

The co-regulation data(Figure 5.4) showed increasing group-dependent differences in co-regulation over session 1 which culminated in a mean systematic disruption in stimulus-response behaviour by the ACTIVE group volunteers. The findings of Study 1 suggested that a significant variation in the co-regulation of skill parameters could signal a disruption in the the stimulus-response strategy required during early motor learning. In fact, in respect of the analysis of control strategy in Fitts' type tasks, this finding has some prior precedents.

The relative behavioural emphasis towards movement rate or spatial variability in a task has been referred to as behavioural bias (Guiard and Olafsdottir, 2011)and has been the subject of recent experimental research (Elliott, Hansen and Grierson, 2009; MacKenzie and Isokoski, 2008; Bootsma, Fernandez and Mottet, 2004). Human motor control and adaption to environmental perturbations are contingent upon ongoing matching of internal forward models based upon previous sensory experiences of variability in relation to behavioural goals (Shadmehr, Smith and Krakauer, 2010). Fluent, rapid motor control is known to depend upon the accuracy of internally generated, predictive forward models which, through experience of motor behaviours can account for sensorimotor noise (random effects) and the systematic effects of changes in the internal and external environment (Shadmehr, Smith and Krakauer, 2010; Todorov, 2004). Thus, motor output and sensory experience are intimately associated in optimisation of goal-centric motor performance (van Beers, 2009) and the development of more sophisticated motor engrams(Novick and Vaadia, 2011).

The literature suggests that both healthy and cognitively-impaired patient groups can produce comparable skilled outcomes based upon indexes of performance I_P -a parameter upon which our TPR is directly based. But pathological groups may only able to achieve this by increasing movement rates to compensate for a significantly higher net spatial error rate (Simmons *et al.*, 2011). In the presence of significantly more spatial errors in performance of cyclic motor tasks, faster end-point velocities between fixed points suggest that increased movement rates can be

a viable strategy to maintain information transfer rates in compensating for innate deficits in spatial accuracy (Simmons *et al.*, 2011; Smits-Engelsman *et al.*, 2003) albeit a more energetic strategy.

In general, effective motor control strategies balance the balance between muscle properties, delays in sensorimotor transmission and the requirement for stability (Todorov, 2004). In healthy persons, kinetic and kinematic refinement in upper limb functionality is a viable strategy for the preservation of goal success in fatigued states (Missenard, Mottet and Perrey, 2009), perhaps because reductions in movement rate allow more time for address the effects of random motor noise upon reaching actions (van Beers, 2009).In pathological states characterised by deficits in visuomotor integration and coordination disorder (Simmons *et al.*, 2011; Smits-Engelsman *et al.*, 2003; Wilson *et al.*, 2001)the pattern of behaviour towards *increased* movement rates appears driven by the impairment of predictive open-loop internal models, a feed-forward discrepancy between the expected and actual reaching endpoints arising from an difficulty in processing sensory information (Wilson *et al.*, 2001). Such individuals, who are subject to greater levels of net spatial end-point error, appear able to implicitly apply effective alternate systematic strategies to return motor skill outcomes to healthy norm levels despite the occurrence of more targeting errors (Smits-Engelsman *et al.*, 2003). Thus, even substantially impaired sensorimotor systems can develop effective strategies for modulating movement rates, in order to deal with spatial error optimally.

These empirically-derived insights, in the current context suggest that disruption of regulation between the stimulus (spatial error) and response (motor output) might precipitate the formation of successful compensatory adaptions in behaviour. The current analysis of linear co-regulation suggests that at the follow-up session both groups appeared to fall back on a direct, on-line stimulus response mechanism for effective motor control (Figure 5.4) to achieve an effectively identical level of learned success in skilled performance. The ability to achieve the same behavioural outcome using alternate kinematic strategies is entirely consistent with the theory of motor abundance, whereby the many redundant degrees of freedom available in upper limb motion can be recruited to solve changing internal and external environmental conditions to achieve the same behavioural goal (Latash, 2012).

5.7.8 Possible underlying mechanisms

Taken together, the current results suggest that the disruption of stimulus-response behaviour in Session 1 may have affected the formation of action-dependent forward models, resulting in

a significant relative deficit in skill outcome at the beginning of Session 2 and with later, lasting divergences in the pattern of corticomotor plasticity. The intervention of anodal tDCS acts in a non-focal way, with the electrode pads overlying large areas of the sensorimotor cortex. Anodal tDCS, when applied in the current configuration has been shown to modulate neuronal activity across widespread areas of the brain, including the sensorimotor cortex and premotor cortices (Lang *et al.*, 2005) and so we cannot discount that mechanisms acting across multiple brain areas might give rise to such complex effects.

Modulation of the excitability of different cortical areas can differentially affect the ability to perform and learn motor skills. Enhancement of activity in M1 with anodal tDCS could drive increases in muscle contraction in a directly mechanistic way, because M1 has been shown to be important in the processing of temporal, rather than spatial aspects of skilled activity (Lin *et al.*, 2009). Activity in M1, both at the level of the individual neuron and the network, codes for the kinematic and kinetic attributes of changing position and joint moment over time, rather than spatial mapping (Schwartz, 2007). M1 is known to be particularly active in the intertrial interval during practise of skilled motor tasks (Lin *et al.*, 2010) suggesting a learning process subserving the laying down of lasting motor memories involved in subsequent skilled performance (Monfils, Plautz and Kleim, 2005). But perturbation of M1 excitability with inhibitory theta burst TMS, either during the early stages of learning or the consolidation of the motor memory did not affect subsequent performance (Platz *et al.*, 2012a; Platz *et al.*, 2012b) supporting the notion that, although neurons in M1 encode for position and movement the processes underlying the laying down of memory in this area of the brain do not occur in M1 (Shemmell *et al.*, 2007).

Modulating the excitability of these or other areas of the brain could potentially have a number of effects on motor planning and control. For example, the closely adjacent S1 area of the brain may be important both for spatial mapping and the formation of motor skill. Anatomical studies in the macaque suggest that the area 3a of S1 acts as an integration centre for multisensory information and feedback from the motor system (Jones and Porter, 1980; Huffman and Krubitzer, 2001a; Heath, Hore and Phillips, 1976) suggesting that this area is important in generating a common frame of reference for accurate prehension (Huffman and Krubitzer, 2001a). In the non-dominant upper limb, following a prolonged skill training protocol, performance was not contingent upon activity of M1, the primary S1, the premotor cortex or the sensorimotor associative area (Platz *et al.*, 2012b). In contrast, after a period of training from the naïve state, whereas activity in M1 region was only specifically engaged

during enactment of rapid movements, S1 was important for motor performance and learning, (Platz *et al.*, 2012a).

While consolidation of motor learning was not disrupted by perturbation of M1 (Baraduc *et al.*, 2004), perturbation of the S1region with inhibitory TMS during motor practise was shown to have a detrimental impact on the capacity to learn practical manual (Platz *et al.*, 2012a) and spatial tracking tasks (Vidoni *et al.*, 2010) which may be attributable to the impaired capacity to construct accurate forward models (Vidoni *et al.*, 2010). Whether any effect on learning in the current study could have been attributable to increased excitability of S1 is not possible to state, as behavioural experimental study designs evaluate the net effect of interventions rather than the underlying mechanisms (Kendall, 2003). But, because anodal tDCS is a non-focal intervention it is possible that simultaneously increasing the excitability of S1 and M1 non-focally with anodal tDCS during skill learning could have dual effects. While increases in excitability in M1 may enhance motor force output, the concurrent effect upon S1 might be to disrupt the formation of forward models which underpin improvements in motor performance (Krakauer and Shadmehr, 2006).

Another area, the excitability of which could directly be affected by anodal tDCS stimulation is the premotor cortex (PMC). The PMC is a region of the brain which lies in the frontal cortex immediately rostral to M1. It has been associated with processing of sensory and cognitive information from the parietal cortex, supplementary motor areas (SMA) and dorsolateral prefrontal cortex (DLPFC) respectively, and is known to have direct projections to the spinal cord as well as outputs to M1 (Kantak *et al.*, 2012). While dorsal PMC neurons integrate information relating to the hand and the target during planning of movement (Pesaran, Nelson and Andersen, 2006), the ventral premotor cortex (PMv) is important in the planning of grasp and manipulation with the hand. Plasticity in the PMv is thought to be important in recovery of function following stroke and brain injury (Dancause *et al.*, 2005). This area is strongly interconnected with frontal areas including the SMA, the sensory cortex, the parietal areas and the hand area of M1, learning through action observation as part of the mirror neuron system (Vogt *et al.*, 2007)) and, furthermore the caudal area closest to M1 is particularly associated with movement (Simon *et al.*, 2002).

Perturbation of the PMv with rTMS affected the capacity to form a matching grasp pattern on an object (Fogassi *et al.*, 2001) and the grip force on an object previously established through experience (Dafotakis *et al.*, 2008) while PMv exerts on-line control over M1 during reprogramming of movement (Buch *et al.*, 2010). Thus, PMv is thought to be an important

node for processing of the properties important in grasp patterning and force, both prior to and during actioning of the command via M1 (Kantak *et al.*, 2012). Moreover, inhibition of this area with rTMS during a motor learning impaired aiming and placement of large objects, suggesting that the PMC is important for ballistic hand movements in extra-personal space specifically during early skill learning (Platz *et al.*, 2012a) rather than following learning of the task (Platz *et al.*, 2012b).

But is it plausible, that a short-term disruption of performance could determine lasting patterns of cortical plasticity and behaviour? In the absence of internal or external environmental perturbations, computational models and empirical findings predict that the extent of spatial accuracy in reaching is contingent upon the management of motor noise (van Beers, 2009; Van Beers, Haggard and Wolpert, 2004). It has been suggested that the variability of reaching movements is proportional to the magnitude and duration of the force output from the muscle(s) (Sternad *et al.*, 2011; Van Beers, Haggard and Wolpert, 2004; Harris and Wolpert, 1998). The outcome of noise upon reaching trajectory which arises in central planning of the movement (Churchland, Afshar and Shenoy, 2006)is essentially stochastic (Todorov and Jordan, 2002), but the motor noise component can be managed through the optimisation of sub-movements for trajectory correction (Meyer *et al.*, 1988).Thus, the effect of random motor noise alone (as distinct from systematic error which is solved in planning (van Beers, 2009) on reaching error is thought to be proportional to the velocity of the movement (Sternad *et al.*, 2011). But empirically it was found that variability was not directly velocity-dependent, suggestive that there was management of motor noise in a way that optimised error tolerance (Sternad *et al.*, 2011).

An important goal of movement control is to minimise the likelihood of missing the target in the presence of signal-dependent noise (Harris and Wolpert, 1998). It has been suggested that in the presence of perturbations, sensory noise becomes the primary factor in determining the variability of reaching trajectories (Guigon, Baraduc and Desmurget, 2008). Intrusive levels of sensory noise will detrimentally affect the utility of pre-existing forward models (Shadmehr, Smith and Krakauer, 2010). But, with the solution manifold bounded by the composition of stochastic noise, task tolerance and task-specific co-variances, it is possible to produce a net reduction in the extent of dispersion about the idealised target over a succession of movements (Müller and Sternad, 2004). Therefore, there could actually be a behavioural advantage to increasing the movement rate in the presence of sensory noise. Matching the effects of sensory and motor noise through velocity management, to create a synergistic

coupling of the two sources of variance, could result in the best accuracy outcome (Müller and Sternad, 2004; Todorov and Jordan, 2002). Furthermore, alternative strategies may develop to adapt to conditions of poor sensory reliability. In conditions of high quality sensory feedback it has been found that adaption of reaching commands was driven strongly by observation of sensory error, but as sensory feedback degraded, reward prediction became more important to the outcome where adaption of motor commands could also occur through anticipation of the reward (Izawa and Shadmehr, 2011). That is, in conditions of insufficient sensory information the potential for spatial accuracy is limited but the ultimate object of the behaviour, of producing movements that maximise reward, is preserved (Izawa and Shadmehr, 2011).

Modulation of movement rate, through the impedance of successive muscle contractions (Guigon, Baraduc and Desmurget, 2008) must be achieved through sensory observation, utilising observation-based adaption mechanisms. The incorporation of these observations into lasting motor memories (Larssen, Ong and Hodges, 2012) can give rise to persisting differences in the corticomotor connectivity which is thought to underpin use-dependent adaptation (Boroojerdi *et al.*, 2001b). Thus, the experience-dependent model will reflect the sensory observation made during the original compensatory strategy (Novick and Vaadia, 2011). In this fashion it is possible for short-term adaptations to sources of noise during learning to inform lasting motor memories and subsequent behavioural strategies. Such a learning mechanism could support the chronological implications of the current data, whereby the strategies adopted to achieve the goal were divergent and hence resulted in group-specific differences in cortico-spinal excitability to target muscles but both groups appeared equally adept at the behavioural goal of target matching at the follow-up session.

5.8 Limitations of the study

In background TMS studies (VII.2.12.1) we established results confirming previous findings that the excitability of representative proximal muscles (medial deltoid and biceps brachii) is low (Devanne *et al.*, 2006; Wassermann *et al.*, 1992), and concluded that it was not practicable or in the interests of participant comfort to gather resting state SRc from proximal muscles. We therefore rely on the excitability characteristics gathered from cortical representations of the non-dominant medial deltoid muscle when the muscle was in a state of standardised activation. As a general finding, activated muscle states to 20% of MVC, as in the current study have been found to minimise the value of the motor threshold while moderately facilitating

the gain of TMS-evoked MEP responses (Devanne, Lavoie and Capaday, 1997). Higher intensity TMS stimuli evoke responses from cumulatively greater areas of the cortex and so if the largest proportional change in excitability is over the area topographically close to the coil then relatively large changes in response would be seen at lower TMS intensities as we have seen. However, in the current study we used a single 90mm coil for TMS stimulation, which though valid for use in measurement studies applies a relatively non-focal locus of excitation to brain tissues (Badawy *et al.*, 2011). Hence we must interpret our results as suggesting simply that net excitability increased across the muscle representation, or that a new population of cortico-spinal synaptic connections became available for excitation. TMS mapping or other imaging methods are required in order to gather information relating to changes in topography of corticomotor representations.

Recent work has suggested that anodal tDCS has a secondary short-lasting effect on the activity of spinal motor circuits, including those disynaptic circuits at the cervical level necessary for antagonistic activity in the hand (Roche *et al.*, 2009) and lumbar spinal circuits necessary for co-contraction in the tibialis anterior and soleus muscles of the leg (Roche *et al.*, 2011). As the spinal circuits are known sites of training-induced adaption both in health (Duchateau, Semmler and Enoka, 2006) and post-spinal injury (Musienko *et al.*, 2012), there is a potential for the interaction of practise with anodal-tDCS induced excitability modulation at this level.

5.9 Conclusions

No evidence was found to support the alternate hypothesis that anodal tDCS significantly modulated lasting motor skill learning at the follow-up measurement interval 7 days beyond the end of the training period. Likewise, no lasting modulation of corticospinal strength in relation to the resting hand muscle was established at the follow-up interval.

However, the results also revealed that during the training period the learning rate in a complex sequential target matching skill was significantly impaired in healthy persons receiving anodal tDCS compared to the sham control condition. This was preceded by an apparent underlying disruption in the ability to regulate stimulus-response behaviour early in learning. The implications of these findings are that the selection of compensatory behaviours over the short term could have lasting effects upon the lasting plasticity of corticomotor circuits important in the task, thereby influencing future movement strategies. The mechanisms underlying the selection of compensatory behaviours may be the consequence of

increasing the excitability of wide areas of the cortex in a non-focal fashion, and the interaction with the behavioural goal in the specific motor task.

Chapter 6. General Discussion and Conclusions

6.1 General Discussion

The mode of action and observations on the particular characteristics of those subjects whom, in the literature have obtained most benefit led us to question whether a chronic patient group with a remote CNS injury might also gain lasting benefit when anodal tDCS was applied adjunctive to training, whereby tetraplegic spinal cord injured persons might benefit from adjunctive application of this intervention. The data presented is the first to investigate the effect of anodal tDCS on motor learning in an SCI population, and one of a small number of studies suggesting that this intervention might have any effect upon behaviour lasting for a period of days following application.

In general terms, the primary aim of neurorehabilitation is to make a lasting improvement in the acquisition or re-learning of skills following injury (Starkey *et al.*, 2011). Over the decade to date, quite extensive clinical research has questioned the effect of anodal tDCS on motor performance and brain activity in animal models, healthy and neurologically impaired adults following stroke injury to the brain (Bastani and Jaberzadeh, 2012; Nitsche *et al.*, 2008). Anodal tDCS has previously been shown to improve motor skill performance time and response time outcomes in healthy persons and stroke patients, with a general interpretation that an enhancement of aspects of motor learning has taken place (Nitsche *et al.*, 2008; Reis *et al.*, 2008). But the evidence in favour of anodal tDCS as means of improving lasting clinically relevant outcomes in patients or healthy persons is somewhat equivocal (review, Section VII.1.7) and, furthermore does not, in the main, extend beyond an hour past the intervention period (Bastani and Jaberzadeh, 2012). The level of skill attained during rehabilitation training is thought to be an important factor in the lasting benefit following intervention (Merians *et al.*, 2002) and retention of spatial motor skill depends upon implicit motor sequence learning (Ghilardi *et al.*, 2009). The behavioural changes involved in recovery are underpinned by use-dependent neural plasticity within the CNS (Kleim, 2011).

The limitations of existing behavioural outcome-based clinical measurement systems need to be considered (see discussion, Section VIII.5.7.2) because the outcomes of current clinical tests used in human behavioural studies are not compatible with a definition for spatial motor skill based upon a long history of previous findings in motor control research (VII.1.11). Skilled motor performance takes place within the dimensions of time and space, and fundamentally

concerns the capacity to transfer information accurately in achieving spatial behavioural goals. A systematic approach was taken to the development and refinement of measurement systems. It is notable that several research groups have derived measures similar to the TPR outcom, albeit using different terminology – I_P (Fitts, 1954), throughput (MacKenzie and Isokoski, 2008) and the quantity 'q' (Guiard and Olafsdottir, 2011). But to our knowledge, the work presented in Study 1 is the first to recognise the relevance of this parameter as a means of quantifying motor skill states as a univariate outcome, by summarising the relationship between movement and accuracy in terms of goal success. This method might allow researchers to evaluate the outcome of interventions upon motor control and success in the behavioural goal, in a simple but bias-resistant fashion.

In Study 2 a pilot study showed the potential benefit of anodal tDCS to enhance motor function a week following training, though inconsistencies and caveats in the possible effect on outcome measures were highlighted. Notwithstanding the small size and evident heterogeneity of the study sample, these suggested that the effects of the intervention might impart an overall benefit primarily due to improvements in generalizable aspects of activity rather than enhancement of target matching dexterity, which was the central feature of the training task as reflected in the TPR outcome.

In order to investigate the above novel findings while controlling for the problems of recruitment and selection bias outlined above, these findings were further investigated in a relatively homogenous population, by applying a similar experimental protocol in healthy adults. The results of that study determined that there was no significant effect of the intervention on skilled performance at the 7-day follow-up session. As a subsidiary finding, divergent patterns of behaviour and cortical plasticity over time were observed which effectively compensated for intervention-dependent disruption in motor skill outcomes, with the effect of attaining the behavioural performance level several days of memory consolidation time. Comparing these finding back to those of the pilot study where the population was free of brain injury but impaired sensory and motor function, substantial improvements were made in the task-dependent skill outcome measure but which did not emerge until several days following training, compared to gradual improvements during training in a measure not requiring accurate spatial goal attainment (i.e. movement rate in the JTHFT).

The present results only suggest that both intervention groups in both studies were good at learning the skill but that the lasting effect of the experience, coupled with the nature of the

extant sensory and motor capacities in the patient group included in Study 2, had a significantly different effect on the behavioural outcomes following several intervening days. But the finding that, in healthy persons following training and a 48 hour rest period anodal tDCS was shown to have a significant effect upon learning of behaviour hints at a quite profound effect upon the development of forward models involved in learning of the skill. The formation of internal models is explicitly required for development of motor skills in healthy persons (Kawato, 1999) and perhaps even more so following injury to spinal sensory tracts, as the information carrying capacity of the sensory tracts for stimulus-response control is impaired (Darian-Smith, Burman and Darian-Smith, 1999). A number of studies have shown a causal link between upregulation of neural activity by anodal tDCS and BDNF-dependent synaptic plasticity (Antal *et al.*, 2010; Fritsch *et al.*, 2010) thought to underlie motor learning (Li Voti *et al.*, 2011) which are not at all contradicted by the current findings. Rather, it might be that the corticomotor plasticity found in Study 3, and the behavioural plasticity suggested by the results of Study 2, are both the result of interactions between short-term behavioural adaption and memory formation.

If it might be assumed that the same primary effects of anodal tDCS upon cortical excitability operate in both study populations, as brain structures are fully preserved in both groups, then taking the results together it may be that the short-term inhibitory effect of anodal tDCS found during skill training in the healthy population are followed by compensations for disruption of sensorimotor interaction with the behavioural goal. This theory would be supported by the results in the patient population because the predictive or contributory factor underling the lasting enhancement of skilled function in the clinical population studied lies in the severity of the deficit because those already suffering sensorimotor deficits of fine motor control may be less sensitive to the transient disruption of control induced by application of anodal tDCS.

The results of the pilot study showed that the pinprick sensory outcome factor was a significant independent predictor of learning in the TPR skill outcome over the period of study inclusion. Thus, although there were some serious issues which could contribute to bias in the results from that study, the effect of anodal tDCS acted independently of the prevailing net level of sensory uncertainty (or noise) due to the sensory deficit. That is not to say that anodal tDCS may not interact with the sensory deficit to alter the net extent of spatial variability at the target. Because the sum of interacting variances can be less than the contribution of individual variances (Müller and Sternad, 2004) there may actually be a behavioural advantage to matching the sources of sensory and motor noise in order to improve the the goal success

rate in accordance with the motivation instruction (Müller and Sternad, 2004). Hence a combined result of pre-existing and induced sensorimotor noise in the SCI study population could be an increased probability of target matching in the task.

Considering the deficits experienced by the incomplete tetraplegic SCI population with lower cervical lesions, functional control of the shoulder is universally well-preserved while sensory and motor functions of the hand, wrist and elbow can be impaired to varying degrees (Hoffmann *et al.*, 2006). The population is therefore better disposed to improvement in skilled outcomes based upon improved reaching activity, independent of changes in net spatial accuracy at the endpoint of the movement. Notable are findings in stroke and traumatic brain injury patients, kinematic analysis showing that the lasting benefit at 1 year in patients who received dosage of the Arm Ability Training (AAT) modular rehabilitation protocol was mainly attributable to significant increases in the speed of the *primary, ballistic* phase of reaching without significant changes in the secondary, terminal phase of reaching or task accuracy (Platz *et al.*, 2001). And, as previously discussed, the adoption of high movement-rate strategies to compensate for sensorimotor integration issues has been noted in other pathological groups presenting with cognitive disorder (VII.1.8.5). Taken together with the present findings, enhancement of reaching behaviour may well be a valid means of improving behavioural outcomes in populations demonstrating deficits of target matching (Platz *et al.*, 2001) as long as spatial accuracy is not a critical aspect of the activity. But only detailed kinematic studies would be able to successfully investigate intervention-dependent changes in reaching and grasping strategies (Karl, Schneider and Whishaw, 2013).

The significant improvement in the SCI group receiving active anodal tDCS at follow-up may also be related to conditioning factors as well as motor-learning. The notion that anodal tDCS might support extended strength and endurance in motor practise is supported by the literature suggesting short term enhancement of muscle force and stamina independent of experience (Tanaka *et al.*, 2011; Tanaka *et al.*, 2009; Cogiamanian *et al.*, 2007), and our interpretation of the behavioural outcome measures utilised in studies to date (VIII.5.7.2). In healthy functioning, the human motor system is thought to solve prehension problems in the most energy-conservative way through the application of simple rules aided by the smooth progression of kinematics through the end-effector pathway (Yarrow, Brown and Krakauer, 2009; Berret *et al.*, 2011). Kinematic studies confirm that increasing movement rates to achieve shorter reaching times in reaching is underpinned by greater positive and negative joint accelerations, driven by increasing actuating muscle activations involved in the

standardised sequence (Park and Kim, 2008). It is known that acceleration under light, concentric loading conditions demands amongst the highest requirements for muscle activation (Newton *et al.*, 1997), and modulation of motor unit discharge rate to drive muscle force production is also known to be important in sub-maximal motor unit activation (Duchateau, Semmler and Enoka, 2006). Substantial chemical-mechanical energy conversion is necessary for muscle fibre activation (Walsh *et al.*, 2006). Because one of the major aims of skilful movement is thought to be energy efficiency, or achieving the behavioural goal at the lowest cost (Yarrow, Brown and Krakauer, 2009), the implication is that the legacy of the active intervention was towards increased energy expenditure in meeting the same behavioural goals. This could be seen as a net task-specific reduction in energy efficiency. But upper limb task endurance has been shown to be improved by anodal tDCS (Cogiamanian *et al.*, 2007) a benefit which could be useful in reversing fatigue, which is is influenced by factors intrinsic to the CNS (Taylor and Gandevia, 2008) and which is known to limit the basic capacity to undertake activity following spinal cord injury (Hammell *et al.*, 2009). Moreover, strength training in isolation might not improve all aspects of functional performance in daily activities but can improve physical capacity to undertake rehabilitation activities (Hicks *et al.*, 2011) a factor which might be considered in treatment planning as a benefit of the application of anodal tDCS.

The findings of Study 2 suggested a lasting albeit delayed benefit when sensory deficits were factored in, while those from Study 3 represented a relative delay in the rate of motor learning by healthy persons receiving anodal tDCS during training with no effect on lasting retention of the skill at a week beyond training. Taken together, the findings of the current project suggest that there are limitations to the utility of tDCS as an adjunctive rehabilitation intervention. Furthermore, both the nature of the task and the deficits imparted by the presenting pathology may dictate the net advantage conferred by utilisation of the adjunctive therapy in motor rehabilitation, which could have long-lasting consequences. Other studies have also suggested that the benefit imparted by tDCS may not be ubiquitous across clinical populations. For example, the intervention may be less useful in those who suffer primary impairments of activation where the goal of the activity in terms of spatial acuity is vital, such as focal occupational dystonia (Rosenkranz *et al.*, 2009). As an exemplar, a recent study looking at the effect of tDCS modalities on task-dependent sensorimotor retraining in trained pianists found no beneficial effect (Buttkus *et al.*, 2011). Additionally, where gait outcomes are representative of skilled lower limb utilisation, the adjunctive application of anodal tDCS to M1 had no

additional positive effect on functional outcomes, compared to robot-assisted gait training alone (Geroin *et al.*, 2011). Crucially, these activities require acuity of motor control for which simple increases in activity would not be an acceptable compensation.

The positive effects of anodal tDCS revealed by previous studies utilising temporal outcome dimensions alone (discussions: Sections VII.1.7, VIII.5.7.2) might be reconsidered in light of the findings of Study 1, where it was shown that Fitts Law can apply to complex motor tasks, that spatial accuracy is an important factor in spatial skill outcomes and that consideration of task completion time alone may not provide an accurate reflection of skill improvements over time. Factors considered important for the elucidation of the effects of tDCS modalities on spatial motor control include, for example, great care over the use of mechanical interfaces in motor control research. Secondly, when using dependent measures such as reaction time, consideration of effects on the temporal parameter alone could lead to the misattribution of findings otherwise considered representative of learning parameters (Robertson, 2007) when applied to this particular intervention modality.

In summary, researchers and clinicians might consider the limitations and effects of anodal tDCS over different time-scales, the interaction of effects upon the functionality of the participant group of interest over different time scales and perhaps most importantly the dimensions of skilled motor function being captured by measurement instruments tracking the true benefit of the intervention in the dimensions relevant to the study aims.

6.2 General Conclusions

Taken separately and together, the current interventional studies did not provide conclusive evidence that anodal tDCS was effective as a means of modulating the retention of spatial motor tasks, or underlying corticomotor connectivity, at a week beyond the period of training. The main finding of this thesis is that there is insufficient evidence to support anodal tDCS as an effective adjunctive intervention in producing lasting rehabilitation of spatial motor skill from incomplete tetraplegic spinal cord injury.

Previous studies have investigated the effect of anodal tDCS upon limited parameters of motor skill, with improvements in the temporal parameter alone taken as enhancements of motor performance or skill. The current project presents original work showing that it is possible to design integrated task-dependent motor learning and measurement protocols which directly reflect use-dependent changes in task-specific spatial skill and may be less subject to external biases.

To our knowledge this work is also the first to apply and experimentally investigate anodal tDCS as an experimental intervention in rehabilitation of upper limb motor learning in incomplete SCI tetraplegia. The pilot study in a small clinical sample revealed very large effect sizes in favour of the intervention, but which only reached significance when measures of sensory sparing were considered as co-factors. The effects of the intervention were delayed until a week beyond the training period suggesting that there might have been an interaction of short-term inhibitory and longer-term facilitatory effects.

Following up those findings in the relatively homogenous healthy population revealed no lasting effect of anodal tDCS upon learning, although significant between-groups effects upon behaviour were observed at specific intervals during the training period suggesting that the active intervention effectively modified task experience and subsequent learning.

Further research in healthy humans should include larger sample sizes in order to elucidate the extent and time-dependence of the effects of this intervention on behaviour and associated neuroplasticity. Studies in the incomplete tetraplegic SCI population in particular should also include much larger participant samples with more restrictive inclusion criteria where possible, particularly if TMS-evoked outcome measures are to be applied. Study designs in this patient group should also consider factoring in known important predictors of learning. Multicentre trial planning may be required in order to gain access to a sufficiently large population pool of SCI subjects.

The data in the healthy population suggested that plastic time-dependent changes in corticomotor connectivity to proximal and distal muscles took place over, and persisted beyond the period of training. Because such changes may be use-dependent, future studies should investigate the effect of anodal tDCS upon the path and variability of upper limb kinematics involved in reaching and orientation of the grasped object in relation to the target.

Finally, the current studies focused on motor learning in relation to use of the non-dominant upper limb. It is of interest to apply these techniques to investigate learning of skilled tasks in relation to the dominant hand.

6.3 Hypotheses: accepted or rejected

6.3.1.1 $H_1 1$

In tetraplegic iSCI persons, significant task-dependent changes in the primary end-points of the skill-based outcome measure are attributable solely to the adjunctive application of anodal tDCS.

- **Alternate hypothesis rejected.**

6.3.1.2 $H_1 2$

In healthy persons, significant task-dependent changes in the primary behavioural end-points of the study occur and are due to the adjunctive application of anodal tDCS.

- **Alternate hypothesis rejected.**

6.3.1.3 $H_1 3$

In healthy persons, significant lasting changes in TMS-evoked outcome measures occur and are due to the adjunctive application of anodal tDCS.

- **Alternate hypothesis rejected.**

References

Abbott, L.F. and Nelson, S.B. (2000) "Synaptic plasticity: taming the beast", *Nature neuroscience,* vol. 3 Suppl, pp. 1178-1183.

Adkins, D.L., Boychuk, J., Remple, M.S. and Kleim, J.A. (2006) "Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord", *Journal of applied physiology (Bethesda, Md.: 1985),* vol. 101, no. 6, pp. 1776-1782.

Amalberti, R. (2001) "The paradoxes of almost totally safe transportation systems", *Safety Science,* vol. 37, no. 2-3, pp. 109-126.

Anand, S. and Hotson, J. (2002) "Transcranial magnetic stimulation: neurophysiological applications and safety", *Brain and cognition,* vol. 50, no. 3, pp. 366-386.

Anderson, K.D. (2004) "Targeting recovery: priorities of the spinal cord-injured population", *Journal of neurotrauma,* vol. 21, no. 10, pp. 1371-1383.

Antal, A., Chaieb, L., Moliadze, V., Monte-Silva, K., Poreisz, C., Thirugnanasambandam, N., Nitsche, M.A., Shoukier, M., Ludwig, H. and Paulus, W. (2010) "Brain-derived neurotrophic factor (BDNF) gene polymorphisms shape cortical plasticity in humans.", *Brain stimulation,* vol. 3, no. 4, pp. 230-237.

Armand, J., Olivier, E., Edgley, S.A. and Lemon, R.N. (1997) "Postnatal development of corticospinal projections from motor cortex to the cervical enlargement in the macaque monkey", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 17, no. 1, pp. 251-266.

Ashby, P., Reynolds, C., Wennberg, R., Lozano, A.M. and Rothwell, J. (1999) "On the focal nature of inhibition and facilitation in the human motor cortex", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 110, no. 3, pp. 550-555.

ASIA (2011) *International Standards for Neurological Classification of Spinal Cord Injury Revised 2011*, 2011th edn, ASIA, Chicago.

Badawy, R.A.B., Tarletti, R., Mula, M., Varrasi, C. and Cantello, R. (2011) "The routine circular coil is reliable in paired-TMS studies", *Clinical Neurophysiology,* vol. 122, no. 4, pp. 784-788.

Bagesteiro, L.B. and Sainburg, R.L. (2002) "Handedness: dominant arm advantages in control of limb dynamics", *Journal of neurophysiology,* vol. 88, no. 5, pp. 2408-2421.

Baraduc, P., Lang, N., Rothwell, J.C. and Wolpert, D.M. (2004) "Consolidation of Dynamic Motor Learning Is Not Disrupted by rTMS of Primary Motor Cortex", *Current Biology,* vol. 14, no. 3, pp. 252-256.

Barak, S. and Duncan, P.W. (2006) "Issues in Selecting Outcome Measures to Assess Functional Recovery After Stroke", *NeuroRx,* vol. 3, no. 4, pp. 505-524.

Bareyre, F.M., Kerschensteiner, M., Raineteau, O., Mettenleiter, T.C., Weinmann, O. and Schwab, M.E. (2004) "The injured spinal cord spontaneously forms a new intraspinal circuit in adult rats", *Nature neuroscience,* vol. 7, no. 3, pp. 269-277.

Barker, A.T. (1999) "The history and basic principles of magnetic nerve stimulation", *Electroencephalography and clinical neurophysiology.Supplement,* vol. 51, pp. 3-21.

Barker, A.T., Jalinous, R. and Freeston, I.L. (1985) "Non-invasive magnetic stimulation of human motor cortex", *Lancet,* vol. 1, no. 8437, pp. 1106-1107.

Bartlett, R., Wheat, J. and Robins, M. (2007) "Is movement variability important for sports biomechanists?", *Sports Biomechanics,* vol. 6, no. 2, pp. 224-243.

Bastani, A. and Jaberzadeh, S. (2012) "Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: A systematic review and meta-analysis", *Clinical Neurophysiology,* vol. 123, no. 4, pp. 644-657.

Bawa, P. and Lemon, R.N. (1993) "Recruitment of motor units in response to transcranial magnetic stimulation in man", *The Journal of physiology,* vol. 471, pp. 445-464.

Beekhuizen, K.S. and Field-Fote, E.C. (2008) "Sensory stimulation augments the effects of massed practice training in persons with tetraplegia", *Archives of Physical Medicine and Rehabilitation,* vol. 89, no. 4, pp. 602-608.

Beekhuizen, K.S. and Field-Fote, E.C. (2005) "Massed practice versus massed practice with stimulation: effects on upper extremity function and cortical plasticity in individuals with incomplete cervical spinal cord injury", *Neurorehabilitation and neural repair,* vol. 19, no. 1, pp. 33-45.

Beggs, W.D. and Howarth, C.I. (1970) "Movement control in a repetitive motor task", *Nature,* vol. 225, no. 5234, pp. 752-753.

Beggs, W.D.A. and Howarth, C.I. (1972) "The accuracy of aiming at a target : Some further evidence for a theory of intermittent control", *Acta Psychologica,* vol. 36, no. 3, pp. 171-177.

Behm, D.G. and Sale, D.G. (1993) "Intended rather than actual movement velocity determines velocity-specific training response", *Journal of applied physiology (Bethesda, Md.: 1985),* vol. 74, no. 1, pp. 359-368.

Belci, M., Catley, M., Husain, M., Frankel, H.L. and Davey, N.J. (2004) "Magnetic brain stimulation can improve clinical outcome in incomplete spinal cord injured patients", *Spinal cord : the official journal of the International Medical Society of Paraplegia,* vol. 42, no. 7, pp. 417-419.

Berret, B., Chiovetto, E., Nori, F. and Pozzo, T. (2011) "Evidence for composite cost functions in arm movement planning: an inverse optimal control approach", *PLoS computational biology,* vol. 7, no. 10, pp. e1002183.

Bienenstock, E.L., Cooper, L.N. and Munro, P.W. (1982) "Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 2, no. 1, pp. 32-48.

Bikson, M., Datta, A. and Elwassif, M. (2009) "Establishing safety limits for transcranial direct current stimulation", *Clinical Neurophysiology,* vol. 120, no. 6, pp. 1033-1034.

Bikson, M., Inoue, M., Akiyama, H., Deans, J.K., Fox, J.E., Miyakawa, H. and Jefferys, J.G. (2004) "Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro", *The Journal of physiology,* vol. 557, no. Pt 1, pp. 175-190.

Binkofski, F., Loebig, M., Jauch-Chara, K., Bergmann, S., Melchert, U.H., Scholand-Engler, H.G., Schweiger, U., Pellerin, L. and Oltmanns, K.M. (2011) "Brain energy consumption induced by electrical stimulation promotes systemic glucose uptake", *Biological psychiatry,* vol. 70, no. 7, pp. 690-695.

Binsted, G., Chua, R., Helsen, W. and Elliott, D. (2001) "Eye-hand coordination in goal-directed aiming", *Human movement science,* vol. 20, no. 4-5, pp. 563-585.

Birkenmeier, R.L., Prager, E.M. and Lang, C.E. (2010) "Translating animal doses of task-specific training to people with chronic stroke in 1-hour therapy sessions: A proof-of-concept study", *Neurorehabilitation and neural repair,* vol. 24, no. 7, pp. 620-635.

Bizzi, E., Cheung, V.C., d'Avella, A., Saltiel, P. and Tresch, M. (2008) "Combining modules for movement", *Brain Research Reviews,* vol. 57, no. 1, pp. 125-133.

Blennerhassett, J.M., Carey, L.M. and Matyas, T.A. (2008) "Clinical measures of handgrip limitation relate to impaired pinch grip force control after stroke", *Journal of hand therapy : official journal of the American Society of Hand Therapists,* vol. 21, no. 3, pp. 245-252.

Boggio, P.S., Castro, L.O., Savagim, E.A., Braite, R., Cruz, V.C., Rocha, R.R., Rigonatti, S.P., Silva, M.T. and Fregni, F. (2006a) "Enhancement of non-dominant hand motor function by anodal transcranial direct current stimulation", *Neuroscience letters,* vol. 404, no. 1-2, pp. 232-236.

Boggio, P.S., Ferrucci, R., Rigonatti, S.P., Covre, P., Nitsche, M., Pascual-Leone, A. and Fregni, F. (2006b) "Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease", *Journal of the neurological sciences,* vol. 249, no. 1, pp. 31-38.

Boggio, P.S., Nunes, A., Rigonatti, S.P., Nitsche, M.A., Pascual-Leone, A. and Fregni, F. (2007) "Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients", *Restorative Neurology and Neuroscience,* vol. 25, no. 2, pp. 123-129.

Boland, M.R., Spigelman, T. and Uhl, T.L. (2008) "The Function of Brachioradialis", *The Journal of hand surgery,* vol. 33, no. 10, pp. 1853-1859.

Bolognini, N., Pascual-Leone, A. and Fregni, F. (2009) "Using non-invasive brain stimulation to augment motor training-induced plasticity", *Journal of NeuroEngineering and Rehabilitation,* vol. 6, no. 1.

Bolognini, N., Vallar, G., Casati, C., Latif, L.A., El-Nazer, R., Williams, J., Banco, E., MacEa, D.D., Tesio, L., Chessa, C. and Fregni, F. (2011) "Neurophysiological and behavioral effects of tDCS combined with constraint-induced movement therapy in poststroke patients", *Neurorehabilitation and neural repair,* vol. 25, no. 9, pp. 819-829.

Bongers, R.M., Fernandez, L. and Bootsma, R.J. (2009) "Linear and Logarithmic Speed-Accuracy Trade-offs in Reciprocal Aiming Result From Task-Specific Parameterization of an Invariant Underlying Dynamics", *Journal of Experimental Psychology: Human Perception and Performance,* vol. 35, no. 5, pp. 1443-1457.

Bootsma, R.J., Fernandez, L. and Mottet, D. (2004) "Behind Fitts' law: kinematic patterns in goal-directed movements", *International Journal of Human-Computer Studies,* vol. 61, no. 6, pp. 811-821.

Boroojerdi, B., Battaglia, F., Muellbacher, W. and Cohen, L.G. (2001a) "Mechanisms influencing stimulus-response properties of the human corticospinal system", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 112, no. 5, pp. 931-937.

Boroojerdi, B., Ziemann, U., Chen, R., Bütefisch, C.M. and Cohen, L.G. (2001b) "Mechanisms underlying human motor system plasticity", *Muscle and Nerve,* vol. 24, no. 5, pp. 602-613.

Boros, K., Poreisz, C., Munchau, A., Paulus, W. and Nitsche, M.A. (2008) "Premotor transcranial direct current stimulation (tDCS) affects primary motor excitability in humans", *The European journal of neuroscience,* vol. 27, no. 5, pp. 1292-1300.

Brenner, E. and Smeets, J.B.J. (2011) "Quickly 'learning' to move optimally", *Experimental Brain Research,* , no. 213, pp. 153-161.

Brochier, T., Spinks, R.L., Umilta, M.A. and Lemon, R.N. (2004) "Patterns of muscle activity underlying object-specific grasp by the macaque monkey", *Journal of neurophysiology,* vol. 92, no. 3, pp. 1770-1782.

Brocke, J., Irlbacher, K., Hauptmann, B., Voss, M. and Brandt, S.A. (2005) "Transcranial magnetic and electrical stimulation compared: Does TES activate intracortical neuronal circuits?", *Clinical Neurophysiology,* vol. 116, no. 12, pp. 2748-2756.

Brodaty, H., Kemp, N.M. and Low, L.F. (2004) "Characteristics of the GPCOG, a screening tool for cognitive impairment", *International journal of geriatric psychiatry,* vol. 19, no. 9, pp. 870-874.

Brodaty, H., Pond, D., Kemp, N.M., Luscombe, G., Harding, L., Berman, K. and Huppert, F.A. (2002) "The GPCOG: a new screening test for dementia designed for general practice", *Journal of the American Geriatrics Society,* vol. 50, no. 3, pp. 530-534.

Brodbelt, A.R. and Stoodley, M.A. (2003) "Post-traumatic syringomyelia: a review", *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia,* vol. 10, no. 4, pp. 401-408.

Brouwer, B., Sale, M.V. and Nordstrom, M.A. (2001) "Asymmetry of motor cortex excitability during a simple motor task: relationships with handedness and manual performance", *Experimental brain research.Experimentelle Hirnforschung.Experimentation cerebrale,* vol. 138, no. 4, pp. 467-476.

Bruce H, D. (2004) "Strategies for stroke rehabilitation", *The Lancet Neurology,* vol. 3, no. 9, pp. 528-536.

Bruehlmeier, M., Dietz, V., Leenders, K.L., Roelcke, U., Missimer, J. and Curt, A. (1998) "How does the human brain deal with a spinal cord injury?", *The European journal of neuroscience,* vol. 10, no. 12, pp. 3918-3922.

Brunel University London. (2012) *Brunel University Research Ethics Committee homepage*. Available at: http://intranet.brunel.ac.uk/registry/minutes/researchethics/home.shtml (Accessed: 07/26 2012).

Brunoni, A.R., Amadera, J., Berbel, B., Volz, M.S., Rizzerio, B.G. and Fregni, F. (2011) "A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation", *International Journal of Neuropsychopharmacology,* , pp. 1-13.

Bryden, P.J., Roy, E.A. and Spence, J. (2007) "An observational method of assessing handedness in children and adults", *Developmental neuropsychology,* vol. 32, no. 3, pp. 825-846.

Buch, E.R., Mars, R.B., Boorman, E.D. and Rushworth, M.F.S. (2010) "A network centered on ventral premotor cortex exerts both facilitatory and inhibitory control over primary motor cortex during action reprogramming", *Journal of Neuroscience,* vol. 30, no. 4, pp. 1395-1401.

Buddenberg, L.A. and Davis, C. (2000) "Test-retest reliability of the Purdue Pegboard Test", *The American journal of occupational therapy.: official publication of the American Occupational Therapy Association,* vol. 54, no. 5, pp. 555-558.

Bunge, R.P., Puckett, W.R., Becerra, J.L., Marcillo, A. and Quencer, R.M. (1993) "Observations on the pathology of human spinal cord injury. A review and classification of 22 new cases with details from a case of chronic cord compression with extensive focal demyelination", *Advances in Neurology,* vol. 59, pp. 75-89.

Burge, J., Ernst, M.O. and Banks, M.S. (2008) "The statistical determinants of adaptation rate in human reaching", *Journal of Vision,* vol. 8, no. 4, pp. 1-19.

Butefisch, C.M. (2004) "Plasticity in the human cerebral cortex: lessons from the normal brain and from stroke", *The Neuroscientist,* vol. 10, no. 2, pp. 163-173.

Butefisch, C.M., Davis, B.C., Wise, S.P., Sawaki, L., Kopylev, L., Classen, J. and Cohen, L.G. (2000) "Mechanisms of use-dependent plasticity in the human motor cortex", *Proceedings of the National Academy of Sciences of the United States of America,* vol. 97, no. 7, pp. 3661-3665.

Buttkus, F., Baur, V., Jabusch, H.-., De La Cruz Gomez-Pellin, M., Paulus, W., Nitsche, M.A. and Altenmüller, E. (2011) "Single-session tDCS-supported retraining does not improve fine motor control in musician's dystonia", *Restorative Neurology and Neuroscience,* vol. 29, no. 2, pp. 85-90.

Cano-de-la-Cuerda, R., Perez-de-Heredia, M., Miangolarra-Page, J.C., Munoz-Hellin, E. and Fernandez-de-Las-Penas, C. (2010) "Is there muscular weakness in Parkinson's disease?", *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists,* vol. 89, no. 1, pp. 70-76.

Capaday, C. (2004) "The integrated nature of motor cortical function", *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry,* vol. 10, no. 3, pp. 207-220.

Caramia, M.D., Scalise, A., Gordon, R., Michalewski, H.J. and Starr, A. (2000) "Delayed facilitation of motor cortical excitability following repetitive finger movements", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 111, no. 9, pp. 1654-1660.

Carroll, T.J., Riek, S. and Carson, R.G. (2001) "Reliability of the input-output properties of the cortico-spinal pathway obtained from transcranial magnetic and electrical stimulation", *Journal of neuroscience methods,* vol. 112, no. 2, pp. 193-202.

Carroll, T.J., Selvanayagam, V.S., Riek, S. and Semmler, J.G. (2011) "Neural adaptations to strength training: Moving beyond transcranial magnetic stimulation and reflex studies", *Acta Physiologica,* vol. 202, no. 2, pp. 119-140.

Casadio, M., Pressman, A., Fishbach, A., Danziger, Z., Acosta, S., Chen, D., Tseng, H.-. and Mussa-Ivaldi, F.A. (2010) "Functional reorganization of upper-body movement after spinal cord injury", *Experimental Brain Research,* vol. 207, no. 3-4, pp. 233-247.

Chae, J., Yang, G., Park, B.K. and Labatia, I. (2002) "Muscle weakness and cocontraction in upper limb hemiparesis: relationship to motor impairment and physical disability", *Neurorehabilitation and neural repair,* vol. 16, no. 3, pp. 241-248.

Chen, H.M., Chen, C.C., Hsueh, I.P., Huang, S.L. and Hsieh, C.L. (2009) "Test-retest reproducibility and smallest real difference of 5 hand function tests in patients with stroke", *Neurorehabilitation and neural repair,* vol. 23, no. 5, pp. 435-440.

Chen, R., Cros, D., Curra, A., Di Lazzaro, V., Lefaucheur, J.P., Magistris, M.R., Mills, K., Rosler, K.M., Triggs, W.J., Ugawa, Y. and Ziemann, U. (2008) "The clinical diagnostic utility of transcranial magnetic

stimulation: report of an IFCN committee", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 119, no. 3, pp. 504-532.

Chen, R., Yung, D. and Li, J.-. (2003) "Organization of ipsilateral excitatory and inhibitory pathways in the human motor cortex", *Journal of Neurophysiology,* vol. 89, no. 3, pp. 1256-1264.

Churchland, M.M., Afshar, A. and Shenoy, K.V. (2006) "A Central Source of Movement Variability", *Neuron,* vol. 52, no. 6, pp. 1085-1096.

Cieza, A. and Stucki, G. (2008) "The International Classification of Functioning Disability and Health: its development process and content validity", *European journal of physical and rehabilitation medicine,* vol. 44, no. 3, pp. 303-313.

Clark, D.J. and Fielding, R.A. (2012) "Neuromuscular contributions to age-related weakness", *The journals of gerontology.Series A, Biological sciences and medical sciences,* vol. 67, no. 1, pp. 41-47.

Clark, V.P., Coffman, B.A., Mayer, A.R., Weisend, M.P., Lane, T.D.R., Calhoun, V.D., Raybourn, E.M., Garcia, C.M. and Wassermann, E.M. (2012) "TDCS guided using fMRI significantly accelerates learning to identify concealed objects", *NeuroImage,* vol. 59, no. 1, pp. 117-128.

Classen, J., Liepert, J., Wise, S.P., Hallett, M. and Cohen, L.G. (1998) "Rapid plasticity of human cortical movement representation induced by practice", *Journal of neurophysiology,* vol. 79, no. 2, pp. 1117-1123.

Cogiamanian, F., Marceglia, S., Ardolino, G., Barbieri, S. and Priori, A. (2007) "Improved isometric force endurance after transcranial direct current stimulation over the human motor cortical areas", *The European journal of neuroscience,* vol. 26, no. 1, pp. 242-249.

Cohen, J. (1992) "A power primer", *Psychological bulletin,* vol. 112, no. 1, pp. 155-159.

Cohen, L.G., Bandinelli, S., Topka, H.R., Fuhr, P., Roth, B.J. and Hallett, M. (1991) "Topographic maps of human motor cortex in normal and pathological conditions: mirror movements, amputations and spinal cord injuries", *Electroencephalography and clinical neurophysiology.Supplement,* vol. 43, pp. 36-50.

Colebatch, J.G. and Gandevia, S.C. (1989) "The distribution of muscular weakness in upper motor neuron lesions affecting the arm", *Brain : a journal of neurology,* vol. 112, no. 3, pp. 749-763.

Coleman, M.P. and Perry, V.H. (2002) "Axon pathology in neurological disease: a neglected therapeutic target", *Trends in neurosciences,* vol. 25, no. 10, pp. 532-537.

Colyer, R.A. and Kappelman, B. (1981) "Flexor pollicis longus tenodesis in tetraplegia at the sixth cervical level. A prospective evaluation of functional gain", *The Journal of bone and joint surgery.American volume,* vol. 63, no. 3, pp. 376-379.

Constantinescu, A.O., Ilie, A., Moldovan, M. and Stagg, C.J. (2010) "Trans-cranial direct current stimulation (tDCS): A promising new tool to facilitate rehabilitation of manual dexterity after stroke", *Romanian Journal of Neurology/ Revista Romana de Neurologie,* vol. 9, no. 3, pp. 118-123.

Conte, A., Belvisi, D., Iezzi, E., Mari, F., Inghilleri, M. and Berardelli, A. (2008) "Effects of attention on inhibitory and facilitatory phenomena elicited by paired-pulse transcranial magnetic stimulation in healthy subjects", *Experimental Brain Research,* vol. 186, no. 3, pp. 393-399.

Corben, L.A., Tai, G., Wilson, C., Collins, V., Churchyard, A.J. and Delatycki, M.B. (2009) "A comparison of three measures of upper limb function in Friedreich ataxia", *Journal of neurology,* vol. 257, no. 4, pp. 518-523.

Cramer, S.C., Sur, M., Dobkin, B.H., O'Brien, C., Sanger, T.D., Trojanowski, J.Q., Rumsey, J.M., Hicks, R., Cameron, J., Chen, D., Chen, W.G., Cohen, L.G., Decharms, C., Duffy, C.J., Eden, G.F., Fetz, E.E., Filart, R., Freund, M., Grant, S.J., Haber, S., Kalivas, P.W., Kolb, B., Kramer, A.F., Lynch, M., Mayberg, H.S., McQuillen, P.S., Nitkin, R., Pascual-Leone, A., Reuter-Lorenz, P., Schiff, N., Sharma, A., Shekim, L., Stryker, M., Sullivan, E.V. and Vinogradov, S. (2011) "Harnessing neuroplasticity for clinical applications", *Brain,* vol. 134, no. 6, pp. 1591-1609.

Cronin, J., McNair, P.J. and Marshall, R.N. (2001) "Developing explosive power: a comparison of technique and training", *Journal of science and medicine in sport / Sports Medicine Australia,* vol. 4, no. 1, pp. 59-70.

Curt, A., Van Hedel, H.J., Klaus, D., Dietz, V. and EM-SCI Study Group (2008) "Recovery from a spinal cord injury: significance of compensation, neural plasticity, and repair", *Journal of neurotrauma,* vol. 25, no. 6, pp. 677-685.

Dafotakis, M., Sparing, R., Eickhoff, S.B., Fink, G.R. and Nowak, D.A. (2008) "On the role of the ventral premotor cortex and anterior intraparietal area for predictive and reactive scaling of grip force", *Brain research,* vol. 1228, pp. 73-80.

Dancause, N., Barbay, S., Frost, S.B., Plautz, E.J., Chen, D., Zoubina, E.V., Stowe, A.M. and Nudo, R.J. (2005) "Extensive cortical rewiring after brain injury", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 25, no. 44, pp. 10167-10179.

Darian-Smith, I., Burman, K. and Darian-Smith, C. (1999) "Parallel pathways mediating manual dexterity in the macaque", *Experimental brain research.Experimentelle Hirnforschung.Experimentation cerebrale,* vol. 128, no. 1-2, pp. 101-108.

Darling, W.G., Pizzimenti, M.A. and Morecraft, R.J. (2011) "Functional recovery following motor cortex lesions in non-human primates: Experimental implications for human stroke patients", *Journal of Integrative Neuroscience,* vol. 10, no. 3, pp. 353-384.

DaSilva, A.F., Volz, M.S., Bikson, M. and Fregni, F. (2011) "Electrode positioning and montage in transcranial direct current stimulation", *Journal of visualized experiments : JoVE,* vol. (51). pii: 2744. doi, no. 51, pp. 10.3791/2744.

Daskalakis, Z.J., Christensen, B.K., Fitzgerald, P.B. and Chen, R. (2002) "Transcranial magnetic stimulation: a new investigational and treatment tool in psychiatry", *The Journal of neuropsychiatry and clinical neurosciences,* vol. 14, no. 4, pp. 406-415.

Datta, A., Elwassif, M. and Bikson, M. (2009) "Bio-heat transfer model of transcranial DC stimulation: Comparison of conventional pad versus ring electrode", *31st Annual International Conference of the IEEE Engineering in Medicine and Biology Society: Engineering the Future of Biomedicine, EMBC 2009*, pp. 670.

Datta, A., Bansal, V., Diaz, J., Patel, J., Reato, D. and Bikson, M. (2009) "Gyri-precise head model of transcranial direct current stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad", *Brain Stimulation,* vol. 2, no. 4, pp. 201-207.e1.

d'Avella, A., Portone, A., Fernandez, L. and Lacquaniti, F. (2006) "Control of fast-reaching movements by muscle synergy combinations", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 26, no. 30, pp. 7791-7810.

Davey, N.J., Smith, H.C., Savic, G., Maskill, D.W., Ellaway, P.H. and Frankel, H.L. (1999) "Comparison of input-output patterns in the corticospinal system of normal subjects and incomplete spinal cord injured patients", *Experimental brain research.Experimentelle Hirnforschung.Experimentation cerebrale,* vol. 127, no. 4, pp. 382-390.

Day, B.L., Dressler, D., Maertens de Noordhout, A., Marsden, C.D., Nakashima, K., Rothwell, J.C. and Thompson, P.D. (1989) "Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses", *The Journal of physiology,* vol. 412, pp. 449-473.

de Freitas, S.M., Scholz, J.P. and Stehman, A.J. (2007) "Effect of motor planning on use of motor abundance", *Neuroscience letters,* vol. 417, no. 1, pp. 66-71.

De Gennaro, L., Cristiani, R., Bertini, M., Curcio, G., Ferrara, M., Fratello, F., Romei, V. and Rossini, P.M. (2004) "Handedness is mainly associated with an asymmetry of corticospinal excitability and not of transcallosal inhibition", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 115, no. 6, pp. 1305-1312.

de los Reyes-Guzman, A., Gil-Agudo, A., Penasco-Martin, B., Solis-Mozos, M., del Ama-Espinosa, A. and Perez-Rizo, E. (2010) "Kinematic analysis of the daily activity of drinking from a glass in a population with cervical spinal cord injury", *Journal of neuroengineering and rehabilitation,* vol. 7, pp. 41.

De Luca, C.J. (1997) "The use of surface electromyography in biomechanics", *Journal of Applied Biomechanics,* vol. 13, no. 2, pp. 135-163.

De Luca, C.J., Kuznetsov, M., Gilmore, L.D. and Roy, S.H. (2012) "Inter-electrode spacing of surface EMG sensors: Reduction of crosstalk contamination during voluntary contractions", *Journal of Biomechanics,* vol. 45, no. 3, pp. 555-561.

de Vargas Ferreira, V.M., Varoto, R., Azevedo Cacho, E.W. and Cliquet, A.,Jr (2012) "Relationship between function, strength and electromyography of upper extremities of persons with tetraplegia", *Spinal cord,* vol. 50, no. 1, pp. 28-32.

Debas, K., Carrier, J., Orban, P., Barakat, M., Lungu, O., Vandewalle, G., Hadj Tahar, A., Bellec, P., Karni, A., Ungerleider, L.G., Benali, H. and Doyon, J. (2010) "Brain plasticity related to the consolidation of motor sequence learning and motor adaptation", *Proceedings of the National Academy of Sciences of the United States of America,* vol. 107, no. 41, pp. 17839-17844.

Deschenes, M.R., Giles, J.A., McCoy, R.W., Volek, J.S., Gomez, A.L. and Kraemer, W.J. (2002) "Neural factors account for strength decrements observed after short-term muscle unloading", *American journal of physiology. Regulatory, integrative and comparative physiology,* vol. 282, no. 2, pp. 578-583.

Devanne, H., Cassim, F., Ethier, C., Brizzi, L., Thevenon, A. and Capaday, C. (2006) "The comparable size and overlapping nature of upper limb distal and proximal muscle representations in the human motor cortex", *The European journal of neuroscience,* vol. 23, no. 9, pp. 2467-2476.

Devanne, H., Cohen, L.G., Kouchtir-Devanne, N. and Capaday, C. (2002) "Integrated motor cortical control of task-related muscles during pointing in humans", *Journal of neurophysiology,* vol. 87, no. 6, pp. 3006-3017.

Devanne, H., Lavoie, B.A. and Capaday, C. (1997) "Input-output properties and gain changes in the human corticospinal pathway", *Experimental brain research.,* vol. 114, no. 2, pp. 329-338.

Diedrichsen, J., White, O., Newman, D. and Lally, N. (2010) "Use-dependent and error-based learning of motor behaviors", *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience,* vol. 30, no. 15, pp. 5159-5166.

Donnelly, D.J. and Popovich, P.G. (2008) "Inflammation and its role in neuroprotection, axonal regeneration and functional recovery after spinal cord injury", *Experimental neurology,* vol. 209, no. 2, pp. 378-388.

Doyon, J. and Benali, H. (2005) "Reorganization and plasticity in the adult brain during learning of motor skills", *Current opinion in neurobiology,* vol. 15, no. 2, pp. 161-167.

Dragovic, M. (2004) "Towards an improved measure of the Edinburgh Handedness Inventory: a one-factor congeneric measurement model using confirmatory factor analysis", *Laterality,* vol. 9, no. 4, pp. 411-419.

Dragovic, M., Milenkovic, S. and Hammond, G. (2008) "The distribution of hand preference is discrete: A taxometric examination", *British Journal of Psychology,* vol. 99, no. 4, pp. 445-459.

Duchateau, J., Semmler, J.G. and Enoka, R.M. (2006) "Training adaptations in the behavior of human motor units", *Journal of applied physiology,* vol. 101, no. 6, pp. 1766-1775.

Dum, R.P. and Strick, P.L. (1991) "The origin of corticospinal projections from the premotor areas in the frontal lobe", *Journal of Neuroscience,* vol. 11, no. 3, pp. 667-689.

Dundas, J.E., Thickbroom, G.W. and Mastaglia, F.L. (2007) "Perception of comfort during transcranial DC stimulation: effect of NaCl solution concentration applied to sponge electrodes", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 118, no. 5, pp. 1166-1170.

Edwards, M.J., Talelli, P. and Rothwell, J.C. (2008) "Clinical applications of transcranial magnetic stimulation in patients with movement disorders", *The Lancet Neurology,* vol. 7, no. 9, pp. 827-840.

Eliassen, J.C., Souza, T. and Sanes, J.N. (2003) "Experience-Dependent Activation Patterns in Human Brain during Visual-Motor Associative Learning", *Journal of Neuroscience,* vol. 23, no. 33, pp. 10540-10547.

Elliott, D., Chua, R. and Helsen, W.F. (2001) "A century later: Woodworth's (1899) two-component model of goal-directed aiming", *Psychological bulletin,* vol. 127, no. 3, pp. 342-357.

Elliott, D., Hansen, S. and Grierson, L.E. (2009) "Optimising speed and energy expenditure in accurate visually directed upper limb movements", *Ergonomics,* vol. 52, no. 4, pp. 438-447.

Elliott, D., Hansen, S., Grierson, L.E.M., Lyons, J., Bennett, S.J. and Hayes, S.J. (2010) "Goal-Directed Aiming: Two Components but Multiple Processes", *Psychological bulletin,* vol. 136, no. 6, pp. 1023-1044.

Elliott, D., Hansen, S., Mendoza, J. and Tremblay, L. (2004) "Learning to optimize speed, accuracy, and energy expenditure: A framework for understanding speed-accuracy relations in goal-directed aiming", *Journal of motor behavior,* vol. 36, no. 3, pp. 339-351.

Faraway, J. (2003) "Regression modeling of motion with endpoint constraints", *Journal of Visualization and Computer Animation,* vol. 14, no. 1, pp. 31-41.

Field, A. (2005) *Discovering Statistics Using SPSS,* 2nd edn, Sage Publications Ltd., London.

Filho, O.M. (2012) *Pop-up Stopwatch for Microsoft Excel freeware add-in application*. Available at: http://cpap.com.br/orlando/ExcelStopwatchMore.asp?IdC=OrlMoreWin1 (Accessed: 07/18 2012).

Finger, S., Koehler, P.J. and Jagella, C. (2004) "The Monakow concept of diaschisis: origins and perspectives", *Archives of Neurology,* vol. 61, no. 2, pp. 283-288.

Fisher, R.A. (1921) "On the "probable error" of a coefficient of correlation deduced from a small sample.", *Metron,* vol. 1, no. 3-32, pp. 205-235.

Fitts, P.M. (1992) "The information capacity of the human motor system in controlling the amplitude of movement. 1954", *Journal of experimental psychology.General,* vol. 121, no. 3, pp. 262-269.

Fitts, P.M. (1954) "The information capacity of the human motor system in controlling the amplitude of movement", *Journal of experimental psychology,* vol. 47, no. 6, pp. 381-391.

Fitts, P.M. and Radford, B.K. (1966) "Information capacity of discrete motor responses under different cognitive sets", *Journal of experimental psychology,* vol. 71, no. 4, pp. 475-482.

Fling, B.W., Christie, A. and Kamen, G. (2009) "Motor unit synchronization in FDI and biceps brachii muscles of strength-trained males", *Journal of Electromyography and Kinesiology,* vol. 19, no. 5, pp. 800-809.

Fogassi, L., Gallese, V., Buccino, G., Craighero, L., Fadiga, L. and Rizzolatti, G. (2001) "Cortical mechanism for the visual guidance of hand grasping movements in the monkey: A reversible inactivation study", *Brain : a journal of neurology,* vol. 124, no. Pt 3, pp. 571-586.

Frank, E., Wilfurth, S., Landgrebe, M., Eichhammer, P., Hajak, G. and Langguth, B. (2010) "Anodal skin lesions after treatment with transcranial direct current stimulation", *Brain Stimulation,* vol. 3, no. 1, pp. 58-59.

Fregni, F., Boggio, P.S., Mansur, C.G., Wagner, T., Ferreira, M.J., Lima, M.C., Rigonatti, S.P., Marcolin, M.A., Freedman, S.D., Nitsche, M.A. and Pascual-Leone, A. (2005a) "Transcranial direct current stimulation of the unaffected hemisphere in stroke patients", *Neuroreport,* vol. 16, no. 14, pp. 1551-1555.

Fregni, F., Boggio, P.S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., Marcolin, M.A., Rigonatti, S.P., Silva, M.T., Paulus, W. and Pascual-Leone, A. (2005b) "Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory", *Experimental brain research.,* vol. 166, no. 1, pp. 23-30.

Fregni, F., Boggio, P.S., Santos, M.C., Lima, M., Vieira, A.L., Rigonatti, S.P., Silva, M.T., Barbosa, E.R., Nitsche, M.A. and Pascual-Leone, A. (2006a) "Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease", *Movement disorders : official journal of the Movement Disorder Society,* vol. 21, no. 10, pp. 1693-1702.

Fregni, F., Boggio, P.S., Santos, M.C., Lima, M., Vieira, A.L., Rigonatti, S.P., Silva, M.T.A., Barbosa, E.R., Nitsche, M.A. and Pascual-Leone, A. (2006b) "Noninvasive cortical stimulation with transcranial direct current stimulation in Parkinson's disease", *Movement Disorders,* vol. 21, no. 10, pp. 1693-1702.

Fregni, F., Boggio, P.S., Valle, A.C., Rocha, R.R., Duarte, J., Ferreira, M.J., Wagner, T., Fecteau, S., Rigonatti, S.P., Riberto, M., Freedman, S.D. and Pascual-Leone, A. (2006c) "A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients", *Stroke; a journal of cerebral circulation,* vol. 37, no. 8, pp. 2115-2122.

Freund, P., Rothwell, J., Craggs, M., Thompson, A.J. and Bestmann, S. (2011) "Corticomotor representation to a human forearm muscle changes following cervical spinal cord injury", *European Journal of Neuroscience,* vol. 34, no. 11, pp. 1839-1846.

Fricke, K., Seeber, A.A., Thirugnanasambandam, N., Paulus, W., Nitsche, M.A. and Rothwell, J.C. (2011) "Time course of the induction of homeostatic plasticity generated by repeated transcranial direct current stimulation of the human motor cortex", *Journal of neurophysiology,* vol. 105, no. 3, pp. 1141-1149.

Friel, K.M., Heddings, A.A. and Nudo, R.J. (2000) "Effects of postlesion experience on behavioral recovery and neurophysiologic reorganization after cortical injury in primates", *Neurorehabilitation and neural repair,* vol. 14, no. 3, pp. 187-198.

Fritsch, B., Reis, J., Martinowich, K., Schambra, H.M., Ji, Y., Cohen, L.G. and Lu, B. (2010) "Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning", *Neuron,* vol. 66, no. 2, pp. 198-204.

Fujiwara, T., Hara, Y., Akaboshi, K. and Chino, N. (1999) "Relationship between shoulder muscle strength and functional independence measure (FIM) score among C6 tetraplegics", *Spinal Cord,* vol. 37, no. 1, pp. 58-61.

Furlan, J.C., Fehlings, M.G., Tator, C.H. and Davis, A.M. (2008) "Motor and sensory assessment of patients in clinical trials for pharmacological therapy of acute spinal cord injury: Psychometric properties of the ASIA standards", *Journal of neurotrauma,* vol. 25, no. 11, pp. 1273-1301.

Furubayashi, T., Terao, Y., Arai, N., Okabe, S., Mochizuki, H., Hanajima, R., Hamada, M., Yugeta, A., Inomata-Terada, S. and Ugawa, Y. (2008) "Short and long duration transcranial direct current stimulation (tDCS) over the human hand motor area", *Experimental Brain Research,* vol. 185, no. 2, pp. 279-286.

Galea, J.M. and Celnik, P. (2009) "Brain polarization enhances the formation and retention of motor memories", *Journal of neurophysiology,* vol. 102, no. 1, pp. 294-301.

Galea, M.P. and Darian-Smith, I. (1997) "Manual dexterity and corticospinal connectivity following unilateral section of the cervical spinal cord in the macaque monkey", *Journal of Comparative Neurology,* vol. 381, no. 3, pp. 307-319.

Galloway, J.C. and Koshland, G.F. (2002) "General coordination of shoulder, elbow and wrist dynamics during multijoint arm movements", *Experimental brain research.,* vol. 142, no. 2, pp. 163-180.

Garbossa, D., Boido, M., Fontanella, M., Fronda, C., Ducati, A. and Vercelli, A. (2012) "Recent therapeutic strategies for spinal cord injury treatment: possible role of stem cells", *Neurosurgical review,* vol. 35, no. 3, pp. 293-311.

Garry, M.I., Kamen, G. and Nordstrom, M.A. (2004) "Hemispheric differences in the relationship between corticomotor excitability changes following a fine-motor task and motor learning", *Journal of neurophysiology,* vol. 91, no. 4, pp. 1570-1578.

Garry, M.I. and Thomson, R.H. (2009) "The effect of test TMS intensity on short-interval intracortical inhibition in different excitability states", *Experimental brain research.,* vol. 193, no. 2, pp. 267-274.

Gartside, I.B. (1968) "Mechanisms of sustained increases of firing rate of neurones in the rat cerebral cortex after polarization: Reverberating circuits or modification of synaptic conductance? (23)", *Nature,* vol. 220, no. 5165, pp. 382-383.

Gauthier, L.V., Taub, E., Perkins, C., Ortmann, M., Mark, V.W. and Uswatte, G. (2008) "Remodeling the brain: plastic structural brain changes produced by different motor therapies after stroke", *Stroke; a journal of cerebral circulation,* vol. 39, no. 5, pp. 1520-1525.

Georgopoulos, A.P., Kalaska, J.F. and Massey, J.T. (1981) "Spatial trajectories and reaction times of aimed movements: effects of practice, uncertainty, and change in target location", *Journal of neurophysiology,* vol. 46, no. 4, pp. 725-743.

Geroin, C., Picelli, A., Munari, D., Waldner, A., Tomelleri, C. and Smania, N. (2011) "Combined transcranial direct current stimulation and robot-assisted gait training in patients with chronic stroke: A preliminary comparison", *Clinical rehabilitation,* vol. 25, no. 6, pp. 537-548.

Ghilardi, M.F., Moisello, C., Silvestri, G., Ghez, C. and Krakauer, J.W. (2009) "Learning of a sequential motor skill comprises explicit and implicit components that consolidate differently", *Journal of neurophysiology,* vol. 101, no. 5, pp. 2218-2229.

Girgis, J., Merrett, D., Kirkland, S., Metz, G.A., Verge, V. and Fouad, K. (2007) "Reaching training in rats with spinal cord injury promotes plasticity and task specific recovery", *Brain : a journal of neurology,* vol. 130, no. Pt 11, pp. 2993-3003.

Gomez Beldarrain, M., Astorgano, A.G., Gonzalez, A.B. and Garcia-Monco, J.C. (2008) "Sleep improves sequential motor learning and performance in patients with prefrontal lobe lesions", *Clinical neurology and neurosurgery,* vol. 110, no. 3, pp. 245-252.

Goodman, N., Jette, A.M., Houlihan, B. and Williams, S. (2008) "Computer and internet use by persons after traumatic spinal cord injury", *Archives of Physical Medicine and Rehabilitation,* vol. 89, no. 8, pp. 1492-1498.

Gottmann, K., Mittmann, T. and Lessmann, V. (2009) "BDNF signaling in the formation, maturation and plasticity of glutamatergic and GABAergic synapses", *Experimental Brain Research,* vol. 199, no. 3-4, pp. 203-234.

Graves, D.E., Frankiewicz, R.G. and Donovan, W.H. (2006) "Construct validity and dimensional structure of the ASIA motor scale", *Journal of Spinal Cord Medicine,* vol. 29, no. 1, pp. 39-45.

Graziano, M.S.A., Taylor, C.S.R. and Moore, T. (2002) "Complex movements evoked by microstimulation of precentral cortex", *Neuron,* vol. 34, no. 5, pp. 841-851.

Green, J.B., Sora, E., Bialy, Y., Ricamato, A. and Thatcher, R.W. (1998) "Cortical sensorimotor reorganization after spinal cord injury: an electroencephalographic study", *Neurology,* vol. 50, no. 4, pp. 1115-1121.

Griskova, I., Hoppner, J., Ruksenas, O. and Dapsys, K. (2006) "Transcranial magnetic stimulation: the method and application", *Medicina (Kaunas, Lithuania),* vol. 42, no. 10, pp. 798-804.

Guest, J.D., Hiester, E.D. and Bunge, R.P. (2005) "Demyelination and Schwann cell responses adjacent to injury epicenter cavities following chronic human spinal cord injury", *Experimental neurology,* vol. 192, no. 2, pp. 384-393.

Guiard, Y. and Olafsdottir, H.B. (2011) "On the measurement of movement difficulty in the standard approach to fitts' law", *PLoS ONE,* vol. 6, no. 10, pp. e24389.

Guiard, Y., Olafsdottir, H. and Perrault, S. (2011) "Fitts' Law as an Explicit Time/Error Trade-Off", *CHI '11 Proceedings of the 2011 annual conference on Human factors in computing systems*, pp. 1619.

Guigon, E., Baraduc, P. and Desmurget, M. (2008) "Computational motor control: Feedback and accuracy", *European Journal of Neuroscience,* vol. 27, no. 4, pp. 1003-1016.

Gump, A., LeGare, M. and Hunt, D.L. (2002) "Application of Fitts' law to individuals with cerebral palsy", *Perceptual and motor skills,* vol. 94, no. 3 PART 1, pp. 883-895.

Haahr, M. and Haahr, S. (2012) *RANDOM.ORG true random number generation service*. Available at: http://www.random.org/ (Accessed: 07/20 2012).

Hagg, T. and Oudega, M. (2006) "Degenerative and spontaneous regenerative processes after spinal cord injury", *Journal of neurotrauma,* vol. 23, no. 3-4, pp. 264-280.

Hall, K.M., Knudsen, S.T., Wright, J., Charlifue, S.W., Graves, D.E. and Werner, P. (1999) "Follow-up study of individuals with high tetraplegia (C1-C4) 14 to 24 years postinjury", *Archives of Physical Medicine and Rehabilitation,* vol. 80, no. 11, pp. 1507-1513.

Hallett, M. (2000) "Transcranial magnetic stimulation and the human brain", *Nature,* vol. 406, no. 6792, pp. 147-150.

Hammell, K.W., Miller, W.C., Forwell, S.J., Forman, B.E. and Jacobsen, B.A. (2009) "Managing fatigue following spinal cord injury: a qualitative exploration", *Disability and rehabilitation,* vol. 31, no. 17, pp. 1437-1445.

Hamou, C., Shah, N.R., DiPonio, L. and Curtin, C.M. (2009) "Pinch and elbow extension restoration in people with tetraplegia: a systematic review of the literature", *The Journal of hand surgery,* vol. 34, no. 4, pp. 692-699.

Hamzei, F., Liepert, J., Dettmers, C., Weiller, C. and Rijntjes, M. (2006) "Two different reorganization patterns after rehabilitative therapy: an exploratory study with fMRI and TMS", *NeuroImage,* vol. 31, no. 2, pp. 710-720.

Hanson, R.W. and Franklin, M.R. (1976) "Sexual loss in relation to other fuctional losses for spinal cord injured males", *Archives of Physical Medicine and Rehabilitation,* vol. 57, no. 6, pp. 291-293.

Harris, C.M. and Wolpert, D.M. (1998) "Signal-dependent noise determines motor planning", *Nature,* vol. 394, no. 6695, pp. 780-784.

Hauptmann, B. and Karni, A. (2002) "From primed to learn: the saturation of repetition priming and the induction of long-term memory", *Brain research.Cognitive brain research,* vol. 13, no. 3, pp. 313-322.

Heath, C.J., Hore, J. and Phillips, C.G. (1976) "Inputs from low threshold muscle and cutaneous afferents of hand and forearm to areas 3a and 3b of baboon's cerebral cortex", *The Journal of physiology,* vol. 257, no. 1, pp. 199-227.

Heller, A., Wade, D.T., Wood, V.A., Sunderland, A., Hewer, R.L. and Ward, E. (1987) "Arm function after stroke: measurement and recovery over the first three months", *Journal of neurology, neurosurgery, and psychiatry,* vol. 50, no. 6, pp. 714-719.

Herbison, G.J., Isaac, Z., Cohen, M.E. and Ditunno, J.F.,Jr (1996) "Strength post-spinal cord injury: myometer vs manual muscle test", *Spinal cord : the official journal of the International Medical Society of Paraplegia,* vol. 34, no. 9, pp. 543-548.

Herwig, U., Satrapi, P. and Schonfeldt-Lecuona, C. (2003) "Using the international 10-20 EEG system for positioning of transcranial magnetic stimulation", *Brain topography,* vol. 16, no. 2, pp. 95-99.

Hess, C.W., Mills, K.R. and Murray, N.M.F. (1987) "Responses in small hand muscles from magnetic stimulation of the human brain", *Journal of Physiology,* vol. VOL. 388, pp. 397-419.

Hess, G., Aizenman, C.D. and Donoghue, J.P. (1996) "Conditions for the induction of long-term potentiation in layer II/III horizontal connections of the rat motor cortex", *Journal of neurophysiology,* vol. 75, no. 5, pp. 1765-1778.

Hesse, S., Waldner, A., Mehrholz, J., Tomelleri, C., Pohl, M. and Werner, C. (2011) "Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: An exploratory, randomized multicenter trial", *Neurorehabilitation and neural repair,* vol. 25, no. 9, pp. 838-846.

Hesse, S., Werner, C., Schonhardt, E.M., Bardeleben, A., Jenrich, W. and Kirker, S.G. (2007) "Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: a pilot study", *Restorative Neurology and Neuroscience,* vol. 25, no. 1, pp. 9-15.

Hicks, C.M. (2005) *Research Methods for Clinical Therapists: Applied Project Design and Analysis,* 4th edn, Churchill Livingstone, London.

Hicks, A.L., Martin Ginis, K.A., Pelletier, C.A., Ditor, D.S., Foulon, B. and Wolfe, D.L. (2011) "The effects of exercise training on physical capacity, strength, body composition and functional performance among adults with spinal cord injury: a systematic review", *Spinal cord,* vol. 49, no. 11, pp. 1103-1127.

Hill, C.E., Beattie, M.S. and Bresnahan, J.C. (2001) "Degeneration and sprouting of identified descending supraspinal axons after contusive spinal cord injury in the rat", *Experimental neurology,* vol. 171, no. 1, pp. 153-169.

Ho, C.H., Wuermser, L.A., Priebe, M.M., Chiodo, A.E., Scelza, W.M. and Kirshblum, S.C. (2007) "Spinal cord injury medicine. 1. Epidemiology and classification", *Archives of Physical Medicine and Rehabilitation,* vol. 88, no. 3 Suppl 1, pp. S49-54.

Hoffman, L.R. and Field-Fote, E.C. (2007) "Cortical reorganization following bimanual training and somatosensory stimulation in cervical spinal cord injury: a case report", *Physical Therapy,* vol. 87, no. 2, pp. 208-223.

Hoffmann, G., Laffont, I., Hanneton, S. and Roby-Brami, A. (2006) "How to extend the elbow with a weak or paralyzed triceps: control of arm kinematics for aiming in C6-C7 quadriplegic patients", *Neuroscience,* vol. 139, no. 2, pp. 749-765.

Huang, Y.Z., Chen, R.S., Rothwell, J.C. and Wen, H.Y. (2007) "The after-effect of human theta burst stimulation is NMDA receptor dependent", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 118, no. 5, pp. 1028-1032.

Huang, Y.-., Edwards, M.J., Rounis, E., Bhatia, K.P. and Rothwell, J.C. (2005) "Theta burst stimulation of the human motor cortex", *Neuron,* vol. 45, no. 2, pp. 201-206.

Huang, Y.-. and Rothwell, J.C. (2004) "The effect of short-duration bursts of high-frequency, low-intensity transcranial magnetic stimulation on the human motor cortex", *Clinical Neurophysiology,* vol. 115, no. 5, pp. 1069-1075.

Huffman, K.J. and Krubitzer, L. (2001a) "Area 3a: topographic organization and cortical connections in marmoset monkeys", *Cerebral cortex (New York, N.Y.: 1991),* vol. 11, no. 9, pp. 849-867.

Huffman, K.J. and Krubitzer, L. (2001b) "Thalamo-cortical connections of areas 3a and M1 in marmoset monkeys", *Journal of Comparative Neurology,* vol. 435, no. 3, pp. 291-310.

Hummel, F., Celnik, P., Giraux, P., Floel, A., Wu, W.H., Gerloff, C. and Cohen, L.G. (2005) "Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke", *Brain : a journal of neurology,* vol. 128, no. Pt 3, pp. 490-499.

Hummel, F.C. and Cohen, L.G. (2006) "Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke?", *Lancet Neurology,* vol. 5, no. 8, pp. 708-712.

Hummel, F.C., Heise, K., Celnik, P., Floel, A., Gerloff, C. and Cohen, L.G. (2010) "Facilitating skilled right hand motor function in older subjects by anodal polarization over the left primary motor cortex", *Neurobiology of aging,* vol. 31, no. 12, pp. 2160-2168.

Hummel, F.C., Voller, B., Celnik, P., Floel, A., Giraux, P., Gerloff, C. and Cohen, L.G. (2006) "Effects of brain polarization on reaction times and pinch force in chronic stroke", *BMC neuroscience,* vol. 7, pp. 73.

Hunter, T., Sacco, P., Nitsche, M.A. and Turner, D.L. (2009) "Modulation of internal model formation during force field-induced motor learning by anodal transcranial direct current stimulation of primary motor cortex", *Journal of Physiology,* vol. 587, no. 12, pp. 2949-2961.

Huntley, G.W. (1997) "Correlation between patterns of horizontal connectivity and the extend of short-term representational plasticity in rat motor cortex", *Cerebral cortex (New York, N.Y.: 1991),* vol. 7, no. 2, pp. 143-156.

Huys, R. (2012) *Re: 'Fitts' law is not continuous in reciprocal aiming' paper query*, 07/09/2012 edn, E-mail communication.

Huys, R., Fernandez, L., Bootsma, R.J. and Jirsa, V.K. (2010) "Fitts' law is not continuous in reciprocal aiming", *Proceedings of the Royal Society B: Biological Sciences,* vol. 277, no. 1685, pp. 1179-1184.

Illis, L.S. (2011) "Central nervous system regeneration does not occur", *Spinal Cord,* vol. 50, no. 4, pp. 259-263.

Ishida, Y. and Tominaga, T. (2002) "Predictors of neurologic recovery in acute central cervical cord injury with only upper extremity impairment", *Spine,* vol. 27, no. 15, pp. 1652-1658.

Iyer, M.B., Mattu, U., Grafman, J., Lomarev, M., Sato, S. and Wassermann, E.M. (2005) "Safety and cognitive effect of frontal DC brain polarization in healthy individuals", *Neurology,* vol. 64, no. 5, pp. 872-875.

Izawa, J. and Shadmehr, R. (2011) "Learning from sensory and reward prediction errors during motor adaptation", *PLoS computational biology,* vol. 7, no. 3, pp. e1002012.

Jackson, A.B., Dijkers, M., Devivo, M.J. and Poczatek, R.B. (2004) "A demographic profile of new traumatic spinal cord injuries: change and stability over 30 years", *Archives of Physical Medicine and Rehabilitation,* vol. 85, no. 11, pp. 1740-1748.

Jacobs, K.M. and Donoghue, J.P. (1991) "Reshaping the cortical motor map by unmasking latent intracortical connections", *Science (New York, N.Y.),* vol. 251, no. 4996, pp. 944-947.

Jacobson, L., Koslowsky, M. and Lavidor, M. (2012) "TDCS polarity effects in motor and cognitive domains: A meta-analytical review", *Experimental Brain Research,* vol. 216, no. 1, pp. 1-10.

Jacquier-Bret, J., Rezzoug, N. and Gorce, P. (2008) "Synergies during reach-to-grasp: a comparative study between healthy and C6-C7 quadriplegic subjects", *Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society.,* vol. 2008, pp. 5366-5369.

Jäncke, L., Steinmetz, H., Benilow, S. and Ziemann, U. (2004) "Slowing fastest finger movements of the dominant hand with low-frequency rTMS of the hand area of the primary motor cortex", *Experimental Brain Research,* vol. 155, no. 2, pp. 196-203.

Jang, S.H., Ahn, S.H., Byun, W.M., Kim, C.S., Lee, M.Y. and Kwon, Y.H. (2009) "The effect of transcranial direct current stimulation on the cortical activation by motor task in the human brain: An fMRI study", *Neuroscience letters,* vol. 460, no. 2, pp. 117-120.

Jax, S.A., Rosenbaum, D.A. and Vaughan, J. (2007) "Extending Fitts' Law to manual obstacle avoidance", *Experimental Brain Research,* vol. 180, no. 4, pp. 775-779.

Jebsen, R.H., Taylor, N., Trieschmann, R.B., Trotter, M.J. and Howard, L.A. (1969) "An objective and standardized test of hand function", *Archives of Physical Medicine and Rehabilitation,* vol. 50, no. 6, pp. 311-319.

Jeffery, D.T., Norton, J.A., Roy, F.D. and Gorassini, M.A. (2007) "Effects of transcranial direct current stimulation on the excitability of the leg motor cortex", *Experimental Brain Research,* vol. 182, no. 2, pp. 281-287.

Jensen, J.L., Marstrand, P.C. and Nielsen, J.B. (2005a) "Motor skill training and strength training are associated with different plastic changes in the central nervous system", *Journal of applied physiology (Bethesda, Md.: 1985),* vol. 99, no. 4, pp. 1558-1568.

Jensen, J.L., Marstrand, P.C.D. and Nielsen, J.B. (2005b) "Motor skill training and strength training are associated with different plastic changes in the central nervous system", *Journal of applied physiology,* vol. 99, no. 4, pp. 1558-1568.

Jeyaratnam, S. (1992) "Confidence intervals for the correlation coefficient", *Statistics & Probability Letters,* vol. 15, no. 5, pp. 389-393.

Johansson, B.B. (2000) "Brain plasticity and stroke rehabilitation. The Willis lecture", *Stroke; a journal of cerebral circulation,* vol. 31, no. 1, pp. 223-230.

Jones, E.G. and Porter, R. (1980) "What is area 3a?", *Brain research,* vol. 203, no. 1, pp. 1-43.

Jurkiewicz, M.T., Mikulis, D.J., Fehlings, M.G. and Verrier, M.C. (2010) "Sensorimotor cortical activation in patients with cervical spinal cord injury with persisting paralysis", *Neurorehabilitation and neural repair,* vol. 24, no. 2, pp. 136-140.

Jurkiewicz, M.T., Mikulis, D.J., McIlroy, W.E., Fehlings, M.G. and Verrier, M.C. (2007) "Sensorimotor cortical plasticity during recovery following spinal cord injury: a longitudinal fMRI study", *Neurorehabilitation and neural repair,* vol. 21, no. 6, pp. 527-538.

Kaelin-Lang, A., Luft, A.R., Sawaki, L., Burstein, A.H., Sohn, Y.H. and Cohen, L.G. (2002) "Modulation of human corticomotor excitability by somatosensory input", *The Journal of physiology,* vol. 540, no. Pt 2, pp. 623-633.

Kaelin-Lang, A., Sawaki, L. and Cohen, L.G. (2005) "Role of voluntary drive in encoding an elementary motor memory", *Journal of neurophysiology,* vol. 93, no. 2, pp. 1099-1103.

Kakulas, B.A. (2004) "Neuropathology: the foundation for new treatments in spinal cord injury", *Spinal cord : the official journal of the International Medical Society of Paraplegia,* vol. 42, no. 10, pp. 549-563.

Kanagal, S.G. and Muir, G.D. (2009) "Task-dependent compensation after pyramidal tract and dorsolateral spinal lesions in rats", *Experimental neurology,* vol. 216, no. 1, pp. 193-206.

Kang, E.K. and Paik, N.-. (2011) "Effect of a tDCS electrode montage on implicit motor sequence learning in healthy subjects", *Experimental and Translational Stroke Medicine,* vol. 3, no. 1, pp. 4.

Kantak, S.S., Stinear, J.W., Buch, E.R. and Cohen, L.G. (2012) "Rewiring the brain: potential role of the premotor cortex in motor control, learning, and recovery of function following brain injury", *Neurorehabilitation and neural repair,* vol. 26, no. 3, pp. 282-292.

Kantelhardt, S.R., Fadini, T., Finke, M., Kallenberg, K., Siemerkus, J., Bockermann, V., Matthaeus, L., Paulus, W., Schweikard, A., Rohde, V. and Giese, A. (2010) "Robot-assisted image-guided transcranial magnetic stimulation for somatotopic mapping of the motor cortex: a clinical pilot study", *Acta Neurochirurgica,* vol. 152, no. 2, pp. 333-343.

Karl, J.M., Schneider, L.R. and Whishaw, I.Q. (2013) "Nonvisual learning of intrinsic object properties in a reaching task dissociates grasp from reach*", Experimental Brain Research*, vol. 225, no. 4, pp. 465-477.

Karni, A. (1996) "The acquisition of perceptual and motor skills: a memory system in the adult human cortex", *Brain research.Cognitive brain research,* vol. 5, no. 1-2, pp. 39-48.

Karni, A., Meyer, G., Rey-Hipolito, C., Jezzard, P., Adams, M.M., Turner, R. and Ungerleider, L.G. (1998) "The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex", *Proceedings of the National Academy of Sciences of the United States of America,* vol. 95, no. 3, pp. 861-868.

Karni, A. and Sagi, D. (1993) "The time course of learning a visual skill", *Nature,* vol. 365, no. 6443, pp. 250-252.

Katoh, S. and El Masry, W.S. (1995) "Motor recovery of patients presenting with motor paralysis and sensory sparing following cervical spinal cord injuries", *Paraplegia,* vol. 33, no. 9, pp. 506-509.

Kawato, M. (1999) "Internal models for motor control and trajectory planning", *Current opinion in neurobiology,* vol. 9, no. 6, pp. 718-727.

Keele, S.W. (1968) "Movement control in skilled motor performance", *Psychological bulletin,* vol. 70, no. 6, Part 1, pp. 387-403.

Keller, A. (1993) "Intrinsic synaptic organization of the motor cortex", *Cerebral cortex (New York, N.Y.: 1991),* vol. 3, no. 5, pp. 430-441.

Kellor, M., Frost, J., Silberberg, N., Iversen, I. and Cummings, R. (1971) "Hand strength and dexterity", *The American journal of occupational therapy.: official publication of the American Occupational Therapy Association,* vol. 25, no. 2, pp. 77-83.

Kendall, J.M. (2003) "Designing a research project: Randomised controlled trials and their principles", *Emergency Medicine Journal,* vol. 20, no. 2, pp. 164-168.

Khedr, E.M., Abdel-Fadeil, M.R., Farghali, A. and Qaid, M. (2009) "Role of 1 and 3 Hz repetitive transcranial magnetic stimulation on motor function recovery after acute ischaemic stroke", *European journal of neurology : the official journal of the European Federation of Neurological Societies,* vol. 16, no. 12, pp. 1323-1330.

Kidgell, D.J., Stokes, M.A., Castricum, T.J. and Pearce, A.J. (2010) "Neurophysiological responses after short-term strength training of the biceps brachii muscle", *Journal of strength and conditioning research / National Strength & Conditioning Association,* vol. 24, no. 11, pp. 3123-3132.

Kidgell, D.J. and Pearce, A.J. (2010) "Corticospinal properties following short-term strength training of an intrinsic hand muscle", *Human Movement Science,* vol. 29, no. 5, pp. 631-641.

Kiers, L., Clouston, P., Chiappa, K.H. and Cros, D. (1995) "Assessment of cortical motor output: compound muscle action potential versus twitch force recording", *Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control,* vol. 97, no. 2, pp. 131-139.

Kiers, L., Cros, D., Chiappa, K.H. and Fang, J. (1993) "Variability of motor potentials evoked by transcranial magnetic stimulation", *Electroencephalography and Clinical Neurophysiology - Electromyography and Motor Control,* vol. 89, no. 6, pp. 415-423.

Kim, D.Y., Ohn, S.H., Yang, E.J., Park, C.-. and Jung, K.J. (2009) "Enhancing motor performance by anodal transcranial direct current stimulation in subacute stroke patients", *American Journal of Physical Medicine and Rehabilitation,* vol. 88, no. 10, pp. 829-836.

Kim, S.J., Kim, B.K., Ko, Y.J., Bang, M.S., Kim, M.H. and Han, T.R. (2010) "Functional and histologic changes after repeated transcranial direct current stimulation in rat stroke model", *Journal of Korean medical science,* vol. 25, no. 10, pp. 1499-1505.

Kirchberger, I., Biering-Sorensen, F., Charlifue, S., Baumberger, M., Campbell, R., Kovindha, A., Ring, H., Sinnott, A., Scheuringer, M. and Stucki, G. (2010) "Identification of the most common problems in functioning of individuals with spinal cord injury using the International Classification of

Functioning, Disability and Health", *Spinal cord : the official journal of the International Medical Society of Paraplegia,* vol. 48, no. 3, pp. 221-229.

Kirshblum, S.C. and O'Connor, K.C. (1998) "Predicting neurologic recovery in traumatic cervical spinal cord injury", *Archives of Physical Medicine and Rehabilitation,* vol. 79, no. 11, pp. 1456-1466.

Kirton, A., Chen, R., Friefeld, S., Gunraj, C., Pontigon, A.M. and Deveber, G. (2008) "Contralesional repetitive transcranial magnetic stimulation for chronic hemiparesis in subcortical paediatric stroke: a randomised trial", *Lancet neurology,* vol. 7, no. 6, pp. 507-513.

Kleim, J.A. (2011) "Neural plasticity and neurorehabilitation: Teaching the new brain old tricks", *Journal of communication disorders,* vol. 44, no. 5, pp. 521-528.

Kleim, J.A., Hogg, T.M., VandenBerg, P.M., Cooper, N.R., Bruneau, R. and Remple, M. (2004) "Cortical synaptogenesis and motor map reorganization occur during late, but not early, phase of motor skill learning", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 24, no. 3, pp. 628-633.

Klem, G.H., Luders, H.O., Jasper, H.H. and Elger, C. (1999) "The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology", *Electroencephalography and clinical neurophysiology.Supplement,* vol. 52, pp. 3-6.

Kobayashi, M. and Pascual-Leone, A. (2003) "Transcranial magnetic stimulation in neurology", *Lancet neurology,* vol. 2, no. 3, pp. 145-156.

Korman, M., Raz, N., Flash, T. and Karni, A. (2003) "Multiple shifts in the representation of a motor sequence during the acquisition of skilled performance", *Proceedings of the National Academy of Sciences of the United States of America,* vol. 100, no. 21, pp. 12492-12497.

Koshland, G.F., Galloway, J.C. and Farley, B. (2005) "Novel muscle patterns for reaching after cervical spinal cord injury: a case for motor redundancy", *Experimental brain research.,* vol. 164, no. 2, pp. 133-147.

Krajacic, A., Ghosh, M., Puentes, R., Pearse, D.D. and Fouad, K. (2009) "Advantages of delaying the onset of rehabilitative reaching training in rats with incomplete spinal cord injury", *The European journal of neuroscience,* vol. 29, no. 3, pp. 641-651.

Krakauer, J.W. (2006) "Motor learning: its relevance to stroke recovery and neurorehabilitation", *Current opinion in neurology,* vol. 19, no. 1, pp. 84-90.

Krakauer, J.W. and Shadmehr, R. (2006) "Consolidation of motor memory", *Trends in neurosciences,* vol. 29, no. 1, pp. 58-64.

Kuczewski, N., Porcher, C. and Gaiarsa, J.L. (2010) "Activity-dependent dendritic secretion of brain-derived neurotrophic factor modulates synaptic plasticity", *The European journal of neuroscience,* vol. 32, no. 8, pp. 1239-1244.

Kujirai, T., Caramia, M.D., Rothwell, J.C., Day, B.L., Thompson, P.D., Ferbert, A., Wroe, S., Asselman, P. and Marsden, C.D. (1993) "Corticocortical inhibition in human motor cortex", *The Journal of physiology,* vol. 471, pp. 501-519.

Kuo, M.F., Unger, M., Liebetanz, D., Lang, N., Tergau, F., Paulus, W. and Nitsche, M.A. (2008) "Limited impact of homeostatic plasticity on motor learning in humans", *Neuropsychologia,* vol. 46, no. 8, pp. 2122-2128.

Kwon, O.-., Shelton, J.N. and Chiu, G.T.-. (2009) "Single feedback model of human goal-directed movement", *2008 ASME Dynamic Systems and Control Conference, DSCC 2008*ASME Dynamic Systems and Control Division, USA, pp. 953.

Kwon, Y.H. and Jang, S.H. (2011) "The enhanced cortical activation induced by transcranial direct current stimulation during hand movements", *Neuroscience letters,* vol. 492, no. 2, pp. 105-108.

Lang, N., Siebner, H.R., Ernst, D., Nitsche, M.A., Paulus, W., Lemon, R.N. and Rothwell, J.C. (2004) "Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects", *Biological psychiatry,* vol. 56, no. 9, pp. 634-639.

Lang, N., Siebner, H.R., Ward, N.S., Lee, L., Nitsche, M.A., Paulus, W., Rothwell, J.C., Lemon, R.N. and Frackowiak, R.S. (2005) "How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain?", *The European journal of neuroscience,* vol. 22, no. 2, pp. 495-504.

Langhorne, P., Coupar, F. and Pollock, A. (2009) "Motor recovery after stroke: a systematic review", *Lancet neurology,* vol. 8, no. 8, pp. 741-754.

Larssen, B.C., Ong, N.T. and Hodges, N.J. (2012) "Watch and learn: seeing is better than doing when acquiring consecutive motor tasks", *PloS one,* vol. 7, no. 6, pp. e38938.

Larsson, B., Karlsson, S., Eriksson, M. and Gerdle, B. (2003) "Test-retest reliability of EMG and peak torque during repetitive maximum concentric knee extensions", *Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology,* vol. 13, no. 3, pp. 281-287.

Latash, M.L. (2012) "The bliss (not the problem) of motor abundance (not redundancy)", *Experimental Brain Research,* , no. 217, pp. 1-5.

Lawrence, D.G. and Hopkins, D.A. (1976) "The development of motor control in the rhesus monkey: evidence concerning the role of corticomotoneuronal connections", *Brain : a journal of neurology,* vol. 99, no. 2, pp. 235-254.

Lee, T.D., Swanson, L.R. and Hall, A.L. (1991) "What is repeated in a repetition? Effects of practice conditions on motor skill acquisition", *Physical Therapy,* vol. 71, no. 2, pp. 150-156.

Lerman, J. (1996) "Study design in clinical research: Sample size estimation and power analysis", *Canadian Journal of Anaesthesia,* vol. 43, no. 2, pp. 184-191.

Leßmann, V. and Brigadski, T. (2009) "Mechanisms, locations, and kinetics of synaptic BDNF secretion: An update", *Neuroscience research,* vol. 65, no. 1, pp. 11-22.

Lessmann, V., Gottmann, K. and Malcangio, M. (2003) "Neurotrophin secretion: current facts and future prospects", *Progress in neurobiology,* vol. 69, no. 5, pp. 341-374.

Li Voti, P., Conte, A., Suppa, A., Iezzi, E., Bologna, M., Aniello, M.S., Defazio, G., Rothwell, J.C. and Berardelli, A. (2011) "Correlation between cortical plasticity, motor learning and BDNF genotype in healthy subjects", *Experimental brain research.,* vol. 212, no. 1, pp. 91-99.

Li, Y. and Wright, D.L. (2000) "An assessment of the attention demands during random- and blocked-practice schedules", *The Quarterly journal of experimental psychology.A, Human experimental psychology,* vol. 53, no. 2, pp. 591-606.

Liebetanz, D., Koch, R., Mayenfels, S., König, F., Paulus, W. and Nitsche, M.A. (2009) "Safety limits of cathodal transcranial direct current stimulation in rats", *Clinical Neurophysiology,* vol. 120, no. 6, pp. 1161-1167.

Liepert, J., Bauder, H., Wolfgang, H.R., Miltner, W.H., Taub, E. and Weiller, C. (2000) "Treatment-induced cortical reorganization after stroke in humans", *Stroke; a journal of cerebral circulation,* vol. 31, no. 6, pp. 1210-1216.

Liepert, J., Classen, J., Cohen, L.G. and Hallett, M. (1998) "Task-dependent changes of intracortical inhibition", *Experimental brain research.Experimentelle Hirnforschung.Experimentation cerebrale,* vol. 118, no. 3, pp. 421-426.

Liepert, J., Zittel, S. and Weiller, C. (2007) "Improvement of dexterity by single session low-frequency repetitive transcranial magnetic stimulation over the contralesional motor cortex in acute stroke: a double-blind placebo-controlled crossover trial", *Restorative Neurology and Neuroscience,* vol. 25, no. 5-6, pp. 461-465.

Lin, C.H., Fisher, B.E., Wu, A.D., Ko, Y.A., Lee, L.Y. and Winstein, C.J. (2009) "Neural correlate of the contextual interference effect in motor learning: a kinematic analysis", *Journal of motor behavior,* vol. 41, no. 3, pp. 232-242.

Lin, C.H., Winstein, C.J., Fisher, B.E. and Wu, A.D. (2010) "Neural correlates of the contextual interference effect in motor learning: a transcranial magnetic stimulation investigation", *Journal of motor behavior,* vol. 42, no. 4, pp. 223-232.

Loo, C.K., Martin, D.M., Alonzo, A., Gandevia, S., Mitchell, P.B. and Sachdev, P. (2011) "Avoiding skin burns with transcranial direct current stimulation: Preliminary considerations", *International Journal of Neuropsychopharmacology,* vol. 14, no. 3, pp. 425-426.

Lotze, M., Braun, C., Birbaumer, N., Anders, S. and Cohen, L.G. (2003) "Motor learning elicited by voluntary drive", *Brain : a journal of neurology,* vol. 126, no. Pt 4, pp. 866-872.

Lotze, M., Laubis-Herrmann, U. and Topka, H. (2006) "Combination of TMS and fMRI reveals a specific pattern of reorganization in M1 in patients after complete spinal cord injury", *Restorative Neurology and Neuroscience,* vol. 24, no. 2, pp. 97-107.

Lynskey, J.V., Belanger, A. and Jung, R. (2008) "Activity-dependent plasticity in spinal cord injury", *Journal of rehabilitation research and development,* vol. 45, no. 2, pp. 229-240.

Ma, L., Wang, B., Narayana, S., Hazeltine, E., Chen, X., Robin, D.A., Fox, P.T. and Xiong, J. (2010) "Changes in regional activity are accompanied with changes in inter-regional connectivity during 4 weeks motor learning", *Brain research,* vol. 1318, pp. 64-76.

MacKenzie, I.S. and Isokoski, P. (2008) "Fitts' throughput and the speed-accuracy tradeoff", *26th Annual CHI Conference on Human Factors in Computing Systems, CHI 2008*ACM, New York, USA, pp. 1633.

Madhavan, S., Weber II, K.A. and Stinear, J.W. (2011) "Non-invasive brain stimulation enhances fine motor control of the hemiparetic ankle: implications for rehabilitation", *Experimental Brain Research,* vol. 209, no. 1, pp. 9-17.

Maeda, F. and Pascual-Leone, A. (2003) "Transcranial magnetic stimulation: studying motor neurophysiology of psychiatric disorders", *Psychopharmacology,* vol. 168, no. 4, pp. 359-376.

Maier, M.A., Olivier, E., Baker, S.N., Kirkwood, P.A., Morris, T. and Lemon, R.N. (1997) "Direct and indirect corticospinal control of arm and hand motoneurons in the squirrel monkey (Saimiri sciureus)", *Journal of neurophysiology,* vol. 78, no. 2, pp. 721-733.

Malcolm, M.P., Triggs, W.J., Light, K.E., Shechtman, O., Khandekar, G. and Gonzalez Rothi, L.J. (2006) "Reliability of motor cortex transcranial magnetic stimulation in four muscle representations", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 117, no. 5, pp. 1037-1046.

Manger, P.R., Cort, J., Ebrahim, N., Goodman, A., Henning, J., Karolia, M., Rodrigues, S.L. and Strkalj, G. (2008) "Is 21st century neuroscience too focussed on the rat/mouse model of brain function and dysfunction?", *Frontiers in neuroanatomy,* vol. 2, pp. 5.

Marchal-Crespo, L. and Reinkensmeyer, D.J. (2009) "Review of control strategies for robotic movement training after neurologic injury", *Journal of neuroengineering and rehabilitation,* vol. 6, pp. 20-0003-6-20.

Martin, J.H. (2012) "Systems neurobiology of restorative neurology and future directions for repair of the damaged motor systems", *Clinical neurology and neurosurgery,* vol. 114, no. 5, pp. 515-523.

Martinez, M., Brezun, J.M., Zennou-Azogui, Y., Baril, N. and Xerri, C. (2009) "Sensorimotor training promotes functional recovery and somatosensory cortical map reactivation following cervical spinal cord injury", *The European journal of neuroscience,* vol. 30, no. 12, pp. 2356-2367.

Martinez, M., Delcour, M., Russier, M., Zennou-Azogui, Y., Xerri, C., Coq, J.O. and Brezun, J.M. (2010) "Differential tactile and motor recovery and cortical map alteration after C4-C5 spinal hemisection", *Experimental neurology,* vol. 221, no. 1, pp. 186-197.

Mason, C.R., Gomez, J.E. and Ebner, T.J. (2001) "Hand synergies during reach-to-grasp", *Journal of neurophysiology,* vol. 86, no. 6, pp. 2896-2910.

Mathiowetz, V., Weber, K., Kashman, N. and Volland, G. (1985) "Adult norms for the nine hole peg test of finger dexterity", *Occupational Therapy Journal of Research,* vol. 5, no. 1, pp. 24-38.

Matsuo, A., Maeoka, H., Hiyamizu, M., Shomoto, K., Morioka, S. and Seki, K. (2011) "Enhancement of precise hand movement by transcranial direct current stimulation", *Neuroreport,* vol. 22, no. 2, pp. 78-82.

Mattson, S.N., Riley, E.P., Gramling, L., Delis, D.C. and Jones, K.L. (1998) "Neuropsychological comparison of alcohol-exposed children with or without physical features of fetal alcohol syndrome", *Neuropsychology,* vol. 12, no. 1, pp. 146-153.

McDonald, J.W. and Belegu, V. (2006) "Demyelination and remyelination after spinal cord injury", *Journal of neurotrauma,* vol. 23, no. 3-4, pp. 345-359.

McDonald, J.W. and Sadowsky, C. (2002) "Spinal-cord injury", *Lancet,* vol. 359, no. 9304, pp. 417-425.

McDonnell, M.N. and Ridding, M.C. (2006) "Afferent stimulation facilitates performance on a novel motor task", *Experimental Brain Research,* vol. 170, no. 1, pp. 109-115.

McFarland, D.J., Krusienski, D.J., Sarnacki, W.A. and Wolpaw, J.R. (2008) "Emulation of computer mouse control with a noninvasive brain-computer interface", *Journal of neural engineering,* vol. 5, no. 2, pp. 101-110.

McKay, D.R., Ridding, M.C., Thompson, P.D. and Miles, T.S. (2002) "Induction of persistent changes in the organisation of the human motor cortex", *Experimental Brain Research,* vol. 143, no. 3, pp. 342-349.

McKay, W.B., Tuel, S.M., Sherwood, A.M., Stokic, D.S. and Dimitrijevic, M.R. (1995) "Focal depression of cortical excitability induced by fatiguing muscle contraction: a transcranial magnetic stimulation study", *Experimental brain research.Experimentelle Hirnforschung.Experimentation cerebrale,* vol. 105, no. 2, pp. 276-282.

Medendorp, W.P., Beurze, S.M., Van Pelt, S. and Van Der Werf, J. (2008) "Behavioral and cortical mechanisms for spatial coding and action planning", *Cortex; a journal devoted to the study of the nervous system and behavior,* vol. 44, no. 5, pp. 587-597.

Medina, J., Jax, S.A. and Coslett, H.B. (2009) "Two-component models of reaching: evidence from deafferentation in a Fitts' law task", *Neuroscience letters,* vol. 451, no. 3, pp. 222-226.

Melchior, H., Vatine, J.-. and Weiss, P.L. (2007) "Is there a relationship between light touch-pressure sensation and functional hand ability?", *Disability and rehabilitation,* vol. 29, no. 7, pp. 567-575.

Meng, X.-., Rosenthal, R. and Rubin, D.B. (1992) "Comparing correlated correlation coefficients", *Psychological bulletin,* vol. 111, no. 1, pp. 172-175.

Merians, A.S., Jack, D., Boian, R., Tremaine, M., Burdea, G.C., Adamovich, S.V., Recce, M. and Poizner, H. (2002) "Virtual reality-augmented rehabilitation for patients following stroke", *Physical Therapy,* vol. 82, no. 9, pp. 898-915.

Meyer, D.E., Abrams, R.A., Kornblum, S., Wright, C.E. and Smith, J.E.K. (1988) "Optimality in Human Motor Performance: Ideal Control of Rapid Aimed Movements", *Psychological review,* vol. 95, no. 3, pp. 340-370.

Milnik, V. (2009) "Anleitung zur Elektrodenplatzierung des internationalen 10–20-Systems", *Das Neurophysiologie-Labor,* vol. 31, no. 1, pp. 1-35.

Misonou, H., Mohapatra, D.P., Park, E.W., Leung, V., Zhen, D., Misonou, K., Anderson, A.E. and Trimmer, J.S. (2004) "Regulation of ion channel localization and phosphorylation by neuronal activity", *Nature neuroscience,* vol. 7, no. 7, pp. 711-718.

Missenard, O., Mottet, D. and Perrey, S. (2009) "Adaptation of motor behavior to preserve task success in the presence of muscle fatigue", *Neuroscience,* vol. 161, no. 3, pp. 773-786.

Mizuno, M., Yamada, K., He, J., Nakajima, A. and Nabeshima, T. (2003) "Involvement of BDNF receptor TrkB in spatial memory formation", *Learning & memory (Cold Spring Harbor, N.Y.),* vol. 10, no. 2, pp. 108-115.

Moisello, C., Crupi, D., Tunik, E., Quartarone, A., Bove, M., Tononi, G. and Ghilardi, M.F. (2009) "The serial reaction time task revisited: A study on motor sequence learning with an arm-reaching task", *Experimental Brain Research,* vol. 194, no. 1, pp. 143-155.

Moliadze, V., Antal, A. and Paulus, W. (2010) "Electrode-distance dependent after-effects of transcranial direct and random noise stimulation with extracephalic reference electrodes", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 121, no. 12, pp. 2165-2171.

Monaco, S., Kroliczak, G., Quinlan, D.J., Fattori, P., Galletti, C., Goodale, M.A. and Culham, J.C. (2010) "Contribution of visual and proprioceptive information to the precision of reaching movements", *Experimental brain research.,* vol. 202, no. 1, pp. 15-32.

Monfils, M.-., Plautz, E.J. and Kleim, J.A. (2005) "In search of the motor engram: Motor map plasticity as a mechanism for encoding motor experience", *Neuroscientist,* vol. 11, no. 5, pp. 471-483.

Monte-Silva, K., Kuo, M.-., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W. and Nitsche, M.A. (2012) "Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation", *Brain Stimulation,* .

Monzée, J., Lamarre, Y. and Smith, A.M. (2003) "The effects of digital anesthesia on force control using a precision grip", *Journal of neurophysiology,* vol. 89, no. 2, pp. 672-683.

Moritani, T. and deVries, H.A. (1979) "Neural factors versus hypertrophy in the time course of muscle strength gain", *American Journal of Physical Medicine,* vol. 58, no. 3, pp. 115-130.

Morris, R.G.M. (1989) "Synaptic plasticity and learning: Selective impairment of learning in rats and blockade of long-term potentiation in vivo by the N-methyl-D-aspartate receptor antagonist AP5", *Journal of Neuroscience,* vol. 9, no. 9, pp. 3040-3057.

Morris, R.G.M., Anderson, E., Lynch, G.S. and Baudry, M. (1986) "Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5", *Nature,* vol. 319, no. 6056, pp. 774-776.

Muellbacher, W., Ziemann, U., Boroojerdi, B., Cohen, L. and Hallett, M. (2001) "Role of the human motor cortex in rapid motor learning", *Experimental brain research.,* vol. 136, no. 4, pp. 431-438.

Muellbacher, W., Ziemann, U., Wissel, J., Dang, N., Kofler, M., Facchini, S., Boroojerdi, B., Poewe, W. and Hallett, M. (2002) "Early consolidation in human primary motor cortex", *Nature,* vol. 415, no. 6872, pp. 640-644.

Mulcahey, M.J., Hutchinson, D. and Kozin, S. (2007) "Assessment of upper limb in tetraplegia: considerations in evaluation and outcomes research", *Journal of rehabilitation research and development,* vol. 44, no. 1, pp. 91-102.

Muller, H. and Sternad, D. (2009) "Motor learning: changes in the structure of variability in a redundant task", *Advances in Experimental Medicine and Biology,* vol. 629, pp. 439-456.

Müller, H. and Sternad, D. (2009) "Motor learning: changes in the structure of variability in a redundant task.", *Advances in Experimental Medicine and Biology,* vol. 629, pp. 439-456.

Müller, H. and Sternad, D. (2004) "Decomposition of Variability in the Execution of Goal-Oriented Tasks: Three Components of Skill Improvement", *Journal of Experimental Psychology: Human Perception and Performance,* vol. 30, no. 1, pp. 212-233.

Musienko, P., Heutschi, J., Friedli, L., van den Brand, R. and Courtine, G. (2012) "Multi-system neurorehabilitative strategies to restore motor functions following severe spinal cord injury", *Experimental neurology,* vol. 235, no. 1, pp. 100-109.

Nakajima, K., Maier, M.A., Kirkwood, P.A. and Lemon, R.N. (2000) "Striking differences in transmission of corticospinal excitation to upper limb motoneurons in two primate species", *Journal of neurophysiology,* vol. 84, no. 2, pp. 698-709.

Nakamura, H., Kitagawa, H., Kawaguchi, Y. and Tsuji, H. (1997) "Intracortical facilitation and inhibition after transcranial magnetic stimulation in conscious humans", *The Journal of physiology,* vol. 498 (Pt 3), pp. 817-823.

Nakashima, K., Rothwell, J.C., Day, B.L., Thompson, P.D., Shannon, K. and Marsden, C.D. (1989) "Reciprocal inhibition between forearm muscles in patients with writer's cramp and other occupational cramps, symptomatic hemidystonia and hemiparesis due to stroke", *Brain: a journal of neurology,* vol. 112 (Pt 3), pp. 681-697.

Nashmi, R. and Fehlings, M.G. (2001) "Changes in axonal physiology and morphology after chronic compressive injury of the rat thoracic spinal cord", *Neuroscience,* vol. 104, no. 1, pp. 235-251.

National Spinal Cord Injury Statistical Center. (2008) "Spinal cord injury Facts and figures at a glance.", *The journal of spinal cord medicine,* vol. 31, no. 3, pp. 357-358.

Newton, R.U., Murphy, A.J., Humphries, B.J., Wilson, G.J., Kraemer, W.J. and Hakkinen, K. (1997) "Influence of load and stretch shortening cycle on the kinematics, kinetics and muscle activation that occurs during explosive upper-body movements", *European journal of applied physiology and occupational physiology,* vol. 75, no. 4, pp. 333-342.

NHS. (2012) *NHS Health Research Authority National Research Ethics Service*. Available at: http://www.nres.nhs.uk/ (Accessed: 07/26 2012).

Nielsen, J.B. and Cohen, L.G. (2008) "The olympic brain. Does corticospinal plasticity play a role in acquisition of skills required for high-performance sports?", *Journal of Physiology,* vol. 586, no. 1, pp. 65-70.

Nishimura, Y. and Isa, T. (2009) "Compensatory changes at the cerebral cortical level after spinal cord injury", *Neuroscientist,* vol. 15, no. 5, pp. 436-444.

Nishimura, Y. and Isa, T. (2008) "Brain mechanism for functional recovery of finger dexterity after spinal cord injury", *Japanese Journal of Geriatrics,* vol. 45, no. 5, pp. 462-469.

Nishimura, Y., Onoe, H., Morichika, Y., Perfiliev, S., Tsukada, H. and Isa, T. (2007) "Time-dependent central compensatory mechanisms of finger dexterity after spinal cord injury", *Science (New York, N.Y.),* vol. 318, no. 5853, pp. 1150-1155.

Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P.S., Fregni, F. and Pascual-Leone, A. (2008) "Transcranial direct current stimulation: State of the art 2008", *Brain Stimulation,* vol. 1, no. 3, pp. 206-223.

Nitsche, M.A., Doemkes, S., Karaköse, T., Antal, A., Liebetanz, D., Lang, N., Tergau, F. and Paulus, W. (2007) "Shaping the effects of transcranial direct current stimulation of the human motor cortex", *Journal of Neurophysiology,* vol. 97, no. 4, pp. 3109-3117.

Nitsche, M.A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., Henning, S., Tergau, F. and Paulus, W. (2003) "Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans", *Journal of Physiology,* vol. 553, no. 1, pp. 293-301.

Nitsche, M.A., Niehaus, L., Hoffmann, K.T., Hengst, S., Liebetanz, D., Paulus, W. and Meyer, B.-. (2004) "MRI study of human brain exposed to weak direct current stimulation of the frontal cortex", *Clinical Neurophysiology,* vol. 115, no. 10, pp. 2419-2423.

Nitsche, M.A., Nitsche, M.S., Klein, C.C., Tergau, F., Rothwell, J.C. and Paulus, W. (2003) "Level of action of cathodal DC polarisation induced inhibition of the human motor cortex", *Clinical Neurophysiology,* vol. 114, no. 4, pp. 600-604.

Nitsche, M.A. and Paulus, W. (2001) "Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans", *Neurology,* vol. 57, no. 10, pp. 1899-1901.

Nitsche, M.A. and Paulus, W. (2000) "Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation", *Journal of Physiology,* vol. 527, no. 3, pp. 633-639.

Nitsche, M.A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W. and Tergau, F. (2003) "Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human", *Journal of cognitive neuroscience,* vol. 15, no. 4, pp. 619-626.

Nitsche, M.A., Seeber, A., Frommann, K., Klein, C.C., Rochford, C., Nitsche, M.S., Fricke, K., Liebetanz, D., Lang, N., Antal, A., Paulus, W. and Tergau, F. (2005) "Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex", *The Journal of physiology,* vol. 568, no. Pt 1, pp. 291-303.

Nordstrom, M.A. and Butler, S.L. (2002) "Reduced intracortical inhibition and facilitation of corticospinal neurons in musicians", *Experimental brain research.,* vol. 144, no. 3, pp. 336-342.

Noreau, L., Shephard, R.J., Simard, C., Pare, G. and Pomerleau, P. (1993) "Relationship of impairment and functional ability to habitual activity and fitness following spinal cord injury", *International journal of rehabilitation research.,* vol. 16, no. 4, pp. 265-275.

Norenberg, M.D., Smith, J. and Marcillo, A. (2004) "The pathology of human spinal cord injury: defining the problems", *Journal of neurotrauma,* vol. 21, no. 4, pp. 429-440.

Novick, I. and Vaadia, E. (2011) "Just do it: action-dependent learning allows sensory prediction", *PloS one,* vol. 6, no. 10, pp. e26020.

Nudo, R.J., Milliken, G.W., Jenkins, W.M. and Merzenich, M.M. (1996) "Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 16, no. 2, pp. 785-807.

Nudo, R.J., Plautz, E.J. and Milliken, G.W. (1997) "Adaptive Plasticity in Primate Motor Cortex as a Consequence of Behavioral Experience and Neuronal Injury", *Seminars in Neuroscience,* vol. 9, no. 1-2, pp. 13-23.

Oberman, L.M. and Pascual-Leone, A. (2009) "Report of seizure induced by continuous theta burst stimulation", *Brain Stimulation,* vol. 2, no. 4, pp. 246-247.

O'Connor, P.J. (2006) "Trends in spinal cord injury", *Accident; Analysis and Prevention,* vol. 38, no. 1, pp. 71-77.

Okamoto, M., Dan, H., Sakamoto, K., Takeo, K., Shimizu, K., Kohno, S., Oda, I., Isobe, S., Suzuki, T., Kohyama, K. and Dan, I. (2004) "Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10-20 system oriented for transcranial functional brain mapping", *NeuroImage,* vol. 21, no. 1, pp. 99-111.

Oldfield, R.C. (1971) "The assessment and analysis of handedness: the Edinburgh inventory", *Neuropsychologia,* vol. 9, no. 1, pp. 97-113.

Oleson, C.V., Burns, A.S., Ditunno, J.F., Geisler, F.H. and Coleman, W.P. (2005) "Prognostic value of pinprick preservation in motor complete, sensory incomplete spinal cord injury", *Archives of Physical Medicine and Rehabilitation,* vol. 86, no. 5, pp. 988-992.

Olindo, S., Signate, A., Richech, A., Cabre, P., Catonne, Y., Smadja, D. and Pascal-Mousselard, H. (2008) "Quantitative assessment of hand disability by the Nine-Hole-Peg test (9-HPT) in cervical spondylotic myelopathy", *Journal of neurology, neurosurgery, and psychiatry,* vol. 79, no. 8, pp. 965-967.

Olivier, E., Baker, S.N., Nakajima, K., Brochier, T. and Lemon, R.N. (2001) "Investigation into non-monosynaptic corticospinal excitation of macaque upper limb single motor units", *Journal of neurophysiology,* vol. 86, no. 4, pp. 1573-1586.

Ones, K., Yalcinkaya, E.Y., Toklu, B.C. and Caglar, N. (2009) "Effects of age, gender, and cognitive, functional and motor status on functional outcomes of stroke rehabilitation", *NeuroRehabilitation,* vol. 25, no. 4, pp. 241-249.

Otten, E. (2005) "Multi-joint dynamics and the development of movement control", *Neural plasticity,* vol. 12, no. 2-3, pp. 89-98; discussion 263-72.

Oxford Grice, K., Vogel, K.A., Le, V., Mitchell, A., Muniz, S. and Vollmer, M.A. (2003) "Adult norms for a commercially available Nine Hole Peg Test for finger dexterity", *The American Journal of Occupational Therapy,* vol. 57, no. 5, pp. 570-573.

Palm, U., Keeser, D., Schiller, C., Fintescu, Z., Reisinger, E., Padberg, F. and Nitsche, M. (2008) "Skin lesions after treatment with transcranial direct current stimulation (tDCS)", *Brain Stimulation,* vol. 1, no. 4, pp. 386-387.

Park, S. (2002) "Effect of task difficulty on muscle activation patterns during rapid single-joint movements 1", *Perceptual and motor skills,* vol. 94, no. 3 PART 2, pp. 1157-1167.

Park, S. and Kim, M. (2008) "Test of validity of Fitts' index of difficulty as a measure of task difficulty", *Perceptual and motor skills,* vol. 107, no. 3, pp. 901-914.

Parthornratt, T., Parkin, R.M. and Jackson, M. (2011) "Human performance index - a generic performance indicator", *Proceedings of the Institution of Mechanical Engineers. Part I: Journal of Systems and Control Engineering,* vol. 225, no. 6, pp. 721-734.

Pascual-Leone, A., Nguyet, D., Cohen, L.G., Brasil-Neto, J.P., Cammarota, A. and Hallett, M. (1995a) "Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills", *Journal of neurophysiology,* vol. 74, no. 3, pp. 1037-1045.

Pascual-Leone, A., Nguyet, D., Cohen, L.G., Brasil-Neto, J.P., Cammarota, A. and Hallett, M. (1995b) "Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills", *Journal of neurophysiology,* vol. 74, no. 3, pp. 1037-1045.

Pascual-Leone, A., Tarazona, F., Keenan, J., Tormos, J.M., Hamilton, R. and Catala, M.D. (1999) "Transcranial magnetic stimulation and neuroplasticity", *Neuropsychologia,* vol. 37, no. 2, pp. 207-217.

Paulus, W. (2011) "Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods", *Neuropsychological Rehabilitation,* vol. 21, no. 5, pp. 602-617.

Pearce, A.J., Thickbroom, G.W., Byrnes, M.L. and Mastaglia, F.L. (2000) "Functional reorganisation of the corticomotor projection to the hand in skilled racquet players", *Experimental brain research.,* vol. 130, no. 2, pp. 238-243.

Perez, M.A., Lungholt, B.K.S., Nyborg, K. and Nielsen, J.B. (2004) "Motor skill training induces changes in the excitability of the leg cortical area in healthy humans", *Experimental Brain Research,* vol. 159, no. 2, pp. 197-205.

Pesaran, B., Nelson, M.J. and Andersen, R.A. (2006) "Dorsal premotor neurons encode the relative position of the hand, eye, and goal during reach planning", *Neuron,* vol. 51, no. 1, pp. 125-134.

Petersen, N.T., Pyndt, H.S. and Nielsen, J.B. (2003) "Investigating human motor control by transcranial magnetic stimulation", *Experimental brain research.,* vol. 152, no. 1, pp. 1-16.

Platz, T. (2004) "Impairment-oriented training (IOT)--scientific concept and evidence-based treatment strategies", *Restorative Neurology and Neuroscience,* vol. 22, no. 3-5, pp. 301-315.

Platz, T. and Denzler, P. (2002) "Do psychological variables modify motor recovery among patients with mild arm paresis after stroke or traumatic brain injury who receive the Arm Ability Training?", *Restorative Neurology and Neuroscience,* vol. 20, no. 1-2, pp. 37-49.

Platz, T., Roschka, S., Christel, M.I., Duecker, F., Rothwell, J.C. and Sack, A. (2012a) "Early stages of motor skill learning and the specific relevance of the cortical motor system - A combined behavioural training and theta burst TMS study", *Restorative Neurology and Neuroscience,* vol. 30, no. 3, pp. 199-211.

Platz, T., Roschka, S., Doppl, K., Roth, C., Lotze, M., Sack, A.T. and Rothwell, J.C. (2012b) "Prolonged motor skill learning - A combined behavioural training and theta burst TMS study", *Restorative Neurology and Neuroscience,* vol. 30, no. 3, pp. 213-224.

Platz, T., Winter, T., Muller, N., Pinkowski, C., Eickhof, C. and Mauritz, K.H. (2001) "Arm ability training for stroke and traumatic brain injury patients with mild arm paresis: a single-blind, randomized, controlled trial", *Archives of Physical Medicine and Rehabilitation,* vol. 82, no. 7, pp. 961-968.

Polanía, R., Paulus, W., Antal, A. and Nitsche, M.A. (2011) "Introducing graph theory to track for neuroplastic alterations in the resting human brain: A transcranial direct current stimulation study", *NeuroImage,* vol. 54, no. 3, pp. 2287-2296.

Poreisz, C., Boros, K., Antal, A. and Paulus, W. (2007) "Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients", *Brain research bulletin,* vol. 72, no. 4-6, pp. 208-214.

Power, H.A., Norton, J.A., Porter, C.L., Doyle, Z., Hui, I. and Chan, K.M. (2006) "Transcranial direct current stimulation of the primary motor cortex affects cortical drive to human musculature as assessed by intermuscular coherence", *The Journal of physiology,* vol. 577, no. Pt 3, pp. 795-803.

Poynton, A.R., O'Farrell, D.A., Shannon, F., Murray, P., McManus, F. and Walsh, M.G. (1997) "Sparing of sensation to pin prick predicts recovery of a motor segment after injury to the spinal cord", *The Journal of bone and joint surgery.British volume,* vol. 79, no. 6, pp. 952-954.

Prabhu, K., Babu, K.S., Samuel, S. and Chacko, A.G. (2005) "Rapid opening and closing of the hand as a measure of early neurologic recovery in the upper extremity after surgery for cervical spondylotic myelopathy", *Archives of Physical Medicine and Rehabilitation,* vol. 86, no. 1, pp. 105-108.

Pratt, J., Adam, J.J. and Fischer, M.H. (2007) "Visual layout modulates Fitts's law: the importance of first and last positions", *Psychonomic Bulletin and Review,* vol. 14, no. 2, pp. 350-355.

Priori, A., Oliviero, A., Donati, E., Callea, L., Bertolasi, L. and Rothwell, J.C. (1999) "Human handedness and asymmetry of the motor cortical silent period", *Experimental brain research.,* vol. 128, no. 3, pp. 390-396.

Priori, A., Hallett, M. and Rothwell, J.C. (2009) "Repetitive transcranial magnetic stimulation or transcranial direct current stimulation?", *Brain Stimulation,* vol. 2, no. 4, pp. 241-245.

Proteau, L., Marteniuk, R.G., Girouard, Y. and Dugas, C. (1987) "On the type of information used to control and learn an aiming movement after moderate and extensive training", *Human Movement Science,* vol. 6, no. 2, pp. 181-199.

Purpura, D.P. and McMurtry, J.G. (1965) "Intracellular Activities and Evoked Potential Changes during Polarization of Motor Cortex", *Journal of neurophysiology,* vol. 28, pp. 166-185.

Quartarone, A., Rizzo, V., Bagnato, S., Morgante, F., Sant'Angelo, A., Romano, M., Crupi, D., Girlanda, P., Rothwell, J.C. and Siebner, H.R. (2005) "Homeostatic-like plasticity of the primary motor hand area is impaired in focal hand dystonia", *Brain : a journal of neurology,* vol. 128, no. Pt 8, pp. 1943-1950.

Radman, T., Ramos, R.L., Brumberg, J.C. and Bikson, M. (2009) "Role of cortical cell type and morphology in subthreshold and suprathreshold uniform electric field stimulation in vitro", *Brain Stimulation,* vol. 2, no. 4, pp. 215-228.

Radman, T., Su, Y., An, J.H., Parra, L.C. and Bikson, M. (2007) "Spike timing amplifies the effect of electric fields on neurons: implications for endogenous field effects", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 27, no. 11, pp. 3030-3036.

Radojicic, M., Reier, P.J., Steward, O. and Keirstead, H.S. (2005) "Septations in chronic spinal cord injury cavities contain axons", *Experimental neurology,* vol. 196, no. 2, pp. 339-341.

Raineteau, O. and Schwab, M.E. (2001) "Plasticity of motor systems after incomplete spinal cord injury", *Nature reviews.Neuroscience,* vol. 2, no. 4, pp. 263-273.

Ranganathan, R. and Newell, K.M. (2010a) "Emergent flexibility in motor learning", *Experimental brain research.,* vol. 202, no. 4, pp. 755-764.

Ranganathan, R. and Newell, K.M. (2010b) "Influence of motor learning on utilizing path redundancy", *Neuroscience letters,* vol. 469, no. 3, pp. 416-420.

Rathelot, J.A. and Strick, P.L. (2009) "Subdivisions of primary motor cortex based on cortico-motoneuronal cells", *Proceedings of the National Academy of Sciences of the United States of America,* vol. 106, no. 3, pp. 918-923.

Rathelot, J.A. and Strick, P.L. (2006) "Muscle representation in the macaque motor cortex: an anatomical perspective", *Proceedings of the National Academy of Sciences of the United States of America,* vol. 103, no. 21, pp. 8257-8262.

Rebola, N., Srikumar, B.N. and Mulle, C. (2010) "Activity-dependent synaptic plasticity of NMDA receptors", *Journal of Physiology,* vol. 588, no. 1, pp. 93-99.

Reichenbach, A., Bresciani, J.P., Peer, A., Bulthoff, H.H. and Thielscher, A. (2011) "Contributions of the PPC to online control of visually guided reaching movements assessed with fMRI-guided TMS", *Cerebral cortex (New York, N.Y.: 1991),* vol. 21, no. 7, pp. 1602-1612.

Reilly, K.T. and Hammond, G.R. (2006) "Intrinsic hand muscles and digit independence on the preferred and non-preferred hands of humans", *Experimental brain research.Experimentelle Hirnforschung.Experimentation cerebrale,* vol. 173, no. 4, pp. 564-571.

Reis, J., Robertson, E., Krakauer, J.W., Rothwell, J., Marshall, L., Gerloff, C., Wassermann, E., Pascual-Leone, A., Hummel, F., Celnik, P.A., Classen, J., Floel, A., Ziemann, U., Paulus, W., Siebner, H.R., Born, J. and Cohen, L.G. (2008) "Consensus: "Can tDCS and TMS enhance motor learning and memory formation?"", *Brain stimulation,* vol. 1, no. 4, pp. 363-369.

Reis, J., Schambra, H.M., Cohen, L.G., Buch, E.R., Fritsch, B., Zarahn, E., Celnik, P.A. and Krakauer, J.W. (2009) "Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation", *Proc.Natl.Acad.Sci.U.S.A.,* vol. 106, no. 5, pp. 1590-1595.

Reis, J., Swayne, O.B., Vandermeeren, Y., Camus, M., Dimyan, M.A., Harris-Love, M., Perez, M.A., Ragert, P., Rothwell, J.C. and Cohen, L.G. (2008) "Contribution of transcranial magnetic stimulation to the understanding of cortical mechanisms involved in motor control", *Journal of Physiology,* vol. 586, no. 2, pp. 325-351.

Remple, M.S., Bruneau, R.M., VandenBerg, P.M., Goertzen, C. and Kleim, J.A. (2001) "Sensitivity of cortical movement representations to motor experience: evidence that skill learning but not strength training induces cortical reorganization", *Behavioural brain research,* vol. 123, no. 2, pp. 133-141.

Riemann, B.L. and Lephart, S.M. (2002) "The sensorimotor system, part I: The physiologic basis of functional joint stability", *Journal of Athletic Training,* vol. 37, no. 1, pp. 71-79.

Riley, E.P. and McGee, C.L. (2005) "Fetal alcohol spectrum disorders: An overview with emphasis on changes in brain and behavior", *Experimental biology and medicine,* vol. 230, no. 6, pp. 357-365.

Rioult-Pedotti, M.S., Friedman, D., Hess, G. and Donoghue, J.P. (1998) "Strengthening of horizontal cortical connections following skill learning", *Nature neuroscience,* vol. 1, no. 3, pp. 230-234.

Robertson, E.M. (2007) "The serial reaction time task: implicit motor skill learning?", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 27, no. 38, pp. 10073-10075.

Robertson, E.M. and Miall, R.C. (1997) "Multi-joint limbs permit a flexible response to unpredictable events", *Experimental brain research.,* vol. 117, no. 1, pp. 148-152.

Robertson, E.M., Press, D.Z. and Pascual-Leone, A. (2005) "Off-line learning and the primary motor cortex", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 25, no. 27, pp. 6372-6378.

Robinson, M.A., Barton, G.J., Lees, A. and Sett, P. (2010) "Analysis of tetraplegic reaching in their 3D workspace following posterior deltoid-triceps tendon transfer", *Spinal Cord,* vol. 48, no. 8, pp. 619-627.

Roche, N., Lackmy, A., Achache, V., Bussel, B. and Katz, R. (2011) "Effects of anodal transcranial direct current stimulation over the leg motor area on lumbar spinal network excitability in healthy subjects", *Journal of Physiology,* vol. 589, no. 11, pp. 2813-2826.

Roche, N., Lackmy, A., Achache, V., Bussel, B. and Katz, R. (2009) "Impact of transcranial direct current stimulation on spinal network excitability in humans", *Journal of Physiology,* vol. 587, no. 23, pp. 5653-5664.

Roland, M. and Torgerson, D. (1998) "Understanding controlled trials: what outcomes should be measured?", *BMJ (Clinical research ed.),* vol. 317, no. 7165, pp. 1075.

Romanelli, P., Esposito, V., Schaal, D.W. and Heit, G. (2005) "Somatotopy in the basal ganglia: experimental and clinical evidence for segregated sensorimotor channels", *Brain research.Brain research reviews,* vol. 48, no. 1, pp. 112-128.

Rosenkranz, K., Butler, K., Williamon, A. and Rothwell, J.C. (2009) "Regaining motor control in musician's dystonia by restoring sensorimotor organization", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 29, no. 46, pp. 14627-14636.

Rosenkranz, K., Nitsche, M.A., Tergau, F. and Paulus, W. (2000) "Diminution of training-induced transient motor cortex plasticity by weak transcranial direct current stimulation in the human", *Neuroscience letters,* vol. 296, no. 1, pp. 61-63.

Rosenkranz, K., Williamon, A., Butler, K., Cordivari, C., Lees, A.J. and Rothwell, J.C. (2005) "Pathophysiological differences between musician's dystonia and writer's cramp", *Brain : a journal of neurology,* vol. 128, no. Pt 4, pp. 918-931.

Roshan, L., Paradiso, G.O. and Chen, R. (2003) "Two phases of short-interval intracortical inhibition", *Experimental Brain Research,* vol. 151, no. 3, pp. 330-337.

Rosler, K.M. (2001) "Transcranial magnetic brain stimulation: a tool to investigate central motor pathways", *News in physiological sciences : an international journal of physiology produced jointly by the International Union of Physiological Sciences and the American Physiological Society,* vol. 16, pp. 297-302.

Rossi, C., Sallustio, F., Di Legge, S., Stanzione, P. and Koch, G. (2012) "Transcranial direct current stimulation of the affected hemisphere does not accelerate recovery of acute stroke patients", *European Journal of Neurology,* [Online], , pp. 04/04/2012. Available from: doi: 10.1111/j.1468-1331.2012.03703.x. [4 April 2012].

Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A. and Safety of TMS Consensus Group (2009) "Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 120, no. 12, pp. 2008-2039.

Rosti-Otajarvi, E., Hamalainen, P., Koivisto, K. and Hokkanen, L. (2008) "The reliability of the MSFC and its components", *Acta Neurologica Scandinavica,* vol. 117, no. 6, pp. 421-427.

Roth, B.J. (1994) "Mechanisms for electrical stimulation of excitable tissue", *Critical Reviews in Biomedical Engineering,* vol. 22, no. 3-4, pp. 253-305.

Rothwell, J.C., Thompson, P.D., Day, B.L., Dick, J.P.R., Kachi, T., Cowan, J.M.A. and Marsden, C.D. (1987) "Motor cortex stimulation in intact man. I. General characteristics of EMG responses in different muscles", *Brain,* vol. 110, no. 5, pp. 1173-1190.

Sabes, P.N., Jordan, M.I. and Wolpert, D.M. (1998) "The role of inertial sensitivity in motor planning", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 18, no. 15, pp. 5948-5957.

Sadowski, B. (2008) "Plasticity of the cortical motor system", *Journal of Human Kinetics,* vol. 20, no. 1, pp. 5-22.

Sainburg, R.L. and Kalakanis, D. (2000) "Differences in control of limb dynamics during dominant and nondominant arm reaching", *Journal of neurophysiology,* vol. 83, no. 5, pp. 2661-2675.

Sanes, J.N. (2003) "Neocortical mechanisms in motor learning", *Current opinion in neurobiology,* vol. 13, no. 2, pp. 225-231.

Saunders, J.A. and Knill, D.C. (2005) "Humans use continuous visual feedback from the hand to control both the direction and distance of pointing movements", *Experimental Brain Research,* vol. 162, no. 4, pp. 458-473.

Saunders, J.A. and Knill, D.C. (2003) "Humans use continuous visual feedback from the hand to control fast reaching movements", *Experimental Brain Research,* vol. 152, no. 3, pp. 341-352.

Schabowsky, C.N., Hidler, J.M. and Lum, P.S. (2007) "Greater reliance on impedance control in the nondominant arm compared with the dominant arm when adapting to a novel dynamic environment", *Experimental brain research.,* vol. 182, no. 4, pp. 567-577.

Schafer, J.L. and Olsen, M.K. (1998) "Multiple imputation for multivariate missing-data problems: A data analyst's perspective", *Multivariate Behavioral Research,* vol. 33, no. 4, pp. 545-571.

Scheidt, R.A., Reinkensmeyer, D.J., Conditt, M.A., Rymer, W.Z. and Mussa-Ivaldi, F.A. (2000) "Persistence of motor adaptation during constrained, multi-joint, arm movements", *Journal of neurophysiology,* vol. 84, no. 2, pp. 853-862.

Schjetnan, A.G.-. and Escobar, M.L. (2012) "In vivo BDNF modulation of hippocampal mossy fiber plasticity induced by high frequency stimulation", *Hippocampus,* vol. 22, no. 1, pp. 1-8.

Schmidlin, E., Wannier, T., Bloch, J. and Rouiller, E.M. (2004) "Progressive plastic changes in the hand representation of the primary motor cortex parallel incomplete recovery from a unilateral section of the corticospinal tract at cervical level in monkeys", *Brain research,* vol. 1017, no. 1-2, pp. 172-183.

Schmidt, R.A., Zelaznik, H., Hawkins, B., Frank, J.S. and Quinn Jr., J.T. (1979) "Motor-output variability: A theory for the accuracy of rapid motor acts", *Psychological review,* vol. 86, no. 5, pp. 415-451.

Schrader, L.M., Stern, J.M., Fields, T.A., Nuwer, M.R. and Wilson, C.L. (2005) "A lack of effect from transcranial magnetic stimulation (TMS) on the vagus nerve stimulator (VNS)", *Clinical Neurophysiology,* vol. 116, no. 10, pp. 2501-2504.

Schwartz, A.B. (2007) "Useful signals from motor cortex", *The Journal of physiology,* vol. 579, no. Pt 3, pp. 581-601.

Schwartz, S., Cohen, M.E., Herbison, G.J. and Shah, A. (1992) "Relationship between two measures of upper extremity strength: manual muscle test compared to hand-held myometry", *Archives of Physical Medicine and Rehabilitation,* vol. 73, no. 11, pp. 1063-1068.

Sekhon, L.H. and Fehlings, M.G. (2001) "Epidemiology, demographics, and pathophysiology of acute spinal cord injury", *Spine,* vol. 26, no. 24 Suppl, pp. S2-12.

Serrien, D.J. and Spape, M.M. (2009) "The role of hand dominance and sensorimotor congruence in voluntary movement", *Experimental brain research.,* vol. 199, no. 2, pp. 195-200.

Shadmehr, R. and Mussa-Ivaldi, F.A. (1994) "Adaptive representation of dynamics during learning of a motor task", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 14, no. 5 Pt 2, pp. 3208-3224.

Shadmehr, R., Smith, M.A. and Krakauer, J.W. (2010) "Error correction, sensory prediction, and adaptation in motor control", *Annual Review of Neuroscience,* vol. 33, pp. 89-108.

Shemmell, J., Riek, S., Tresilian, J.R. and Carson, R.G. (2007) "The role of the primary motor cortex during skill acquisition on a two-degrees-of-freedom movement task", *Journal of motor behavior,* vol. 39, no. 1, pp. 29-39.

Shimizu, T., Filippi, M.M., Palmieri, M.G., Oliveri, M., Vernieri, F., Pasqualetti, P. and Rossini, P.M. (1999) "Modulation of intracortical excitability for different muscles in the upper extremity: paired magnetic stimulation study with focal versus non-focal coils", *Clinical Neurophysiology,* vol. 110, no. 3, pp. 575-581.

Shimojima, Y., Morita, H., Nishikawa, N., Kodaira, M., Hashimoto, T. and Ikeda, S. (2010) "The safety of transcranial magnetic stimulation with deep brain stimulation instruments", *Parkinsonism & related disorders,* vol. 16, no. 2, pp. 127-131.

Shmuelof, L., Krakauer, J.W. and Mazzoni, P. (2012) "How is a motor skill learned? Change and invariance at the levels of task success and trajectory control", *Journal of neurophysiology,* vol. 108, no. 2, pp. 578-594.

Sibbald, B. and Roland, M. (1998) "Understanding controlled trials. Why are randomised controlled trials important?", *BMJ (Clinical research ed.),* vol. 316, no. 7126, pp. 201.

Siebner, H.R., Lang, N., Rizzo, V., Nitsche, M.A., Paulus, W., Lemon, R.N. and Rothwell, J.C. (2004) "Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: evidence for homeostatic plasticity in the human motor cortex", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 24, no. 13, pp. 3379-3385.

Siebner, H.R. and Rothwell, J. (2003) "Transcranial magnetic stimulation: New insights into representational cortical plasticity", *Experimental Brain Research,* vol. 148, no. 1, pp. 1-16.

Silver, J. (2009) "CNS Regeneration: Only on One Condition", *Current Biology,* vol. 19, no. 11, pp. R444-R446.

Simmons, R.W., Madra, N.J., Levy, S.S., Riley, E.P. and Mattson, S.N. (2011) "Co-regulation of movement speed and accuracy by children with heavy prenatal alcohol exposure.", *Perceptual and motor skills,* vol. 112, no. 1, pp. 172-182.

Simon, S.R., Meunier, M., Piettre, L., Berardi, A.M., Segebarth, C.M. and Boussaoud, D. (2002) "Spatial attention and memory versus motor preparation: premotor cortex involvement as revealed by fMRI", *Journal of neurophysiology,* vol. 88, no. 4, pp. 2047-2057.

Sisto, S.A. and Dyson-Hudson, T. (2007) "Dynamometry testing in spinal cord injury", *Journal of rehabilitation research and development,* vol. 44, no. 1, pp. 123-136.

Sleimen-Malkoun, R., Temprado, J.-., Huys, R., Jirsa, V. and Berton, E. (2012) "Is fitts' law continuous in discrete aiming?", *PLoS ONE,* vol. 7, no. 7, pp. e41190.

Smeets, J.B.J., Van Den Dobbelsteen, J.J., De Grave, D.D.J., Van Beers, R.J. and Brenner, E. (2006) "Sensory integration does not lead to sensory calibration", *Proceedings of the National Academy of Sciences of the United States of America,* vol. 103, no. 49, pp. 18781-18786.

Smith, S., Purzner, T. and Fehlings, M. (2010) "The epidemiology of geriatric spinal cord injury", *Topics in Spinal Cord Injury Rehabilitation,* vol. 15, no. 3, pp. 54-64.

Smits-Engelsman, B.C.M., Wilson, P.H., Westenberg, Y. and Duysens, J. (2003) "Fine motor deficiencies in children with developmental coordination disorder and learning disabilities: An underlying open-loop control deficit", *Human Movement Science,* vol. 22, no. 4-5, pp. 495-513.

Smyth, C., Summers, J.J. and Garry, M.I. (2010) "Differences in motor learning success are associated with differences in M1 excitability", *Human Movement Science,* vol. 29, no. 5, pp. 618-630.

Snoek, G.J., IJzerman, M.J., Hermens, H.J., Maxwell, D. and Biering-Sorensen, F. (2004) "Survey of the needs of patients with spinal cord injury: impact and priority for improvement in hand function in tetraplegics", *Spinal cord : the official journal of the International Medical Society of Paraplegia,* vol. 42, no. 9, pp. 526-532.

Soechting, J.F. (1984) "Effect of target size on spatial and temporal characteristics of a pointing movement in man", *Experimental brain research.,* vol. 54, no. 1, pp. 121-132.

Sohn, M.K., Kim, B.O. and Song, H.T. (2012) "Effect of stimulation polarity of transcranial direct current stimulation on non-dominant hand function", *Annals of Rehabilitation Medicine,* vol. 36, no. 1, pp. 1-7.

Sparing, R., Buelte, D., Meister, I.G., Paus, T. and Fink, G.R. (2008) "Transcranial magnetic stimulation and the challenge of coil placement: a comparison of conventional and stereotaxic neuronavigational strategies", *Human brain mapping,* vol. 29, no. 1, pp. 82-96.

Spooren, A.I., Janssen-Potten, Y.J., Snoek, G.J., Ijzerman, M.J., Kerckhofs, E. and Seelen, H.A. (2008) "Rehabilitation outcome of upper extremity skilled performance in persons with cervical spinal cord injuries", *Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine,* vol. 40, no. 8, pp. 637-644.

Squinto, S.P., Stitt, T.N., Aldrich, T.H., Davis, S., Blanco, S.M., RadzieJewski, C., Glass, D.J., Masiakowski, P., Furth, M.E., Valenzuela, D.M., Distefano, P.S. and Yancopoulos, G.D. (1991) "trkB encodes a functional receptor for brain-derived neurotrophic factor and neurotrophin-3 but not nerve growth factor", *Cell,* vol. 65, no. 5, pp. 885-893.

Stagg, C.J., Bachtiar, V. and Johansen-Berg, H. (2011) "The role of GABA in human motor learning", *Current Biology,* vol. 21, no. 6, pp. 480-484.

Stagg, C.J., Bachtiar, V., O'Shea, J., Allman, C., Bosnell, R.A., Kischka, U., Matthews, P.M. and Johansen-Berg, H. (2012) "Cortical activation changes underlying stimulation-induced behavioural gains in chronic stroke", *Brain,* vol. 135, no. 1, pp. 276-284.

Stagg, C.J., Jayaram, G., Pastor, D., Kincses, Z.T., Matthews, P.M. and Johansen-Berg, H. (2011) "Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning", *Neuropsychologia,* vol. 49, no. 5, pp. 800-804.

Stagg, C.J., O'Shea, J., Kincses, Z.T., Woolrich, M., Matthews, P.M. and Johansen-Berg, H. (2009) "Modulation of movement-associated cortical activation by transcranial direct current stimulation", *The European journal of neuroscience,* vol. 30, no. 7, pp. 1412-1423.

Stark, E., Drori, R. and Abeles, M. (2009) "Motor cortical activity related to movement kinematics exhibits local spatial organization", *Cortex,* vol. 45, no. 3, pp. 418-431.

Starkes, J., Helsen, W. and Elliott, D. (2002) "A menage a trois: the eye, the hand and on-line processing", *Journal of sports sciences,* vol. 20, no. 3, pp. 217-224.

Starkey, M.L., Bleul, C., Maier, I.C. and Schwab, M.E. (2011) "Rehabilitative training following unilateral pyramidotomy in adult rats improves forelimb function in a non-task-specific way", *Experimental neurology,* vol. 232, no. 1, pp. 81-89.

Stern, E.B. (1992) "Stability of the Jebsen-Taylor Hand Function Test across three test sessions.", *The American journal of occupational therapy.: official publication of the American Occupational Therapy Association,* vol. 46, no. 7, pp. 647-649.

Sternad, D., Abe, M.O., Hu, X. and Muller, H. (2011) "Neuromotor noise, error tolerance and velocity-dependent costs in skilled performance", *PLoS computational biology,* vol. 7, no. 9, pp. e1002159.

Streletz, L.J., Belevich, J.K.S., Jones, S.M., Bhushan, A., Shah, S.H. and Herbison, G.J. (1995) "Transcranial magnetic stimulation: Cortical motor maps in acute spinal cord injury", *Brain topography,* vol. 7, no. 3, pp. 245-250.

Stuss, D.T. (2011a) "Functions of the frontal lobes: relation to executive functions", *Journal of the International Neuropsychological Society : JINS,* vol. 17, no. 5, pp. 759-765.

Stuss, D.T. (2011b) "Traumatic brain injury: relation to executive dysfunction and the frontal lobes", *Current opinion in neurology,* vol. 24, no. 6, pp. 584-589.

Sun, Y. and Wong, A.C.M. (2007) "Interval estimation for the normal correlation coefficient", *Statistics and Probability Letters,* vol. 77, no. 17, pp. 1652-1661.

Sunderland, A., Tinson, D., Bradley, L. and Hewer, R.L. (1989) "Arm function after stroke. An evaluation of grip strength as a measure of recovery and a prognostic indicator", *Journal of neurology, neurosurgery, and psychiatry,* vol. 52, no. 11, pp. 1267-1272.

Takeuchi, N., Tada, T., Toshima, M., Chuma, T., Matsuo, Y. and Ikoma, K. (2008) "Inhibition of the unaffected motor cortex by 1 Hz repetitive transcranical magnetic stimulation enhances motor performance and training effect of the paretic hand in patients with chronic stroke", *Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine,* vol. 40, no. 4, pp. 298-303.

Tanaka, S., Hanakawa, T., Honda, M. and Watanabe, K. (2009) "Enhancement of pinch force in the lower leg by anodal transcranial direct current stimulation", *Experimental Brain Research,* vol. 196, no. 3, pp. 459-465.

Tanaka, S., Sandrini, M. and Cohen, L.G. (2011) "Modulation of motor learning and memory formation by non-invasive cortical stimulation of the primary motor cortex", *Neuropsychological Rehabilitation,* vol. 21, no. 5, pp. 650-675.

Tanaka, S., Takeda, K., Otaka, Y., Kita, K., Osu, R., Honda, M., Sadato, N., Hanakawa, T. and Watanabe, K. (2011) "Single session of transcranial direct current stimulation transiently increases knee extensor force in patients with hemiparetic stroke", *Neurorehabilitation and neural repair,* vol. 25, no. 6, pp. 565-569.

Tator, C.H. and Koyanagi, I. (1997) "Vascular mechanisms in the pathophysiology of human spinal cord injury", *Journal of neurosurgery,* vol. 86, no. 3, pp. 483-492.

Taylor, J.L. and Gandevia, S.C. (2008) "A comparison of central aspects of fatigue in submaximal and maximal voluntary contractions", *Journal of applied physiology (Bethesda, Md.: 1985),* vol. 104, no. 2, pp. 542-550.

Taylor, J.L. and Martin, P.G. (2009) "Voluntary motor output is altered by spike-timing-dependent changes in the human corticospinal pathway", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 29, no. 37, pp. 11708-11716.

Tecchio, F., Zappasodi, F., Assenza, G., Tombini, M., Vollaro, S., Barbati, G. and Rossini, P.M. (2010) "Anodal transcranial direct current stimulation enhances procedural consolidation", *Journal of neurophysiology,* vol. 104, no. 2, pp. 1134-1140.

Thickbroom, G.W., Byrnes, M.L. and Mastaglia, F.L. (1999) "A model of the effect of MEP amplitude variation on the accuracy of TMS mapping", *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology,* vol. 110, no. 5, pp. 941-943.

Thickbroom, G.W. and Mastaglia, F.L. (2009) "Plasticity in neurological disorders and challenges for noninvasive brain stimulation (NBS)", *Journal of NeuroEngineering and Rehabilitation,* vol. 6, no. 4.

Thirugnanasambandam, N., Sparing, R., Dafotakis, M., Meister, I.G., Paulus, W., Nitsche, M.A. and Fink, G.R. (2011) "Isometric contraction interferes with transcranial direct current stimulation (tDCS) induced plasticity: evidence of state-dependent neuromodulation in human motor cortex", *Restorative Neurology and Neuroscience,* vol. 29, no. 5, pp. 311-320.

Tinazzi, M., Rosso, T., Zanette, G., Fiaschi, A. and Aglioti, S.M. (2003) "Rapid modulation of cortical proprioceptive activity induced by transient cutaneous deafferentation: neurophysiological evidence of short-term plasticity across different somatosensory modalities in humans", *The European journal of neuroscience,* vol. 18, no. 11, pp. 3053-3060.

Todorov, E. (2004) "Optimality principles in sensorimotor control", *Nature neuroscience,* vol. 7, no. 9, pp. 907-915.

Todorov, E. and Jordan, M.I. (2002) "Optimal feedback control as a theory of motor coordination", *Nature neuroscience,* vol. 5, no. 11, pp. 1226-1235.

Topka, H., Cohen, L.G., Cole, R.A. and Hallett, M. (1991) "Reorganization of corticospinal pathways following spinal cord injury", *Neurology,* vol. 41, no. 8, pp. 1276-1283.

Torgerson, D.J. and Roberts, C. (1999) "Understanding controlled trials. Randomisation methods: concealment", *BMJ (Clinical research ed.),* vol. 319, no. 7206, pp. 375-376.

Totoiu, M.O. and Keirstead, H.S. (2005) "Spinal cord injury is accompanied by chronic progressive demyelination", *The Journal of comparative neurology,* vol. 486, no. 4, pp. 373-383.

Valot, C. and Amalberti, R. (1992) "Metaknowledge for time and reliability", *Reliability Engineering and System Safety,* vol. 36, no. 3, pp. 199-206.

Van Beers, R.J., Haggard, P. and Wolpert, D.M. (2004) "The Role of Execution Noise in Movement Variability", *Journal of neurophysiology,* vol. 91, no. 2, pp. 1050-1063.

van Beers, R.J. (2009) "Motor Learning Is Optimally Tuned to the Properties of Motor Noise", *Neuron,* vol. 63, no. 3, pp. 406-417.

van den Berg, M.E.L., Castellote, J.M., Mahillo-Fernandez, I. and de Pedro-Cuesta, J. (2010) "Incidence of Spinal Cord Injury Worldwide: A Systematic Review", *Neuroepidemiology,* vol. 34, no. 3, pp. 184-192.

van Hedel, H.J., Wirth, B. and Curt, A. (2010) "Ankle motor skill is intact in spinal cord injury, unlike stroke: implications for rehabilitation", *Neurology,* vol. 74, no. 16, pp. 1271-1278.

Van Hedel, H.J.A. and Rudhe, C. (2010) "Motor recovery after spinal cord injury: Assessments, factors and mechanisms", *Schweizerische Rundschau fur Medizin - Praxis,* vol. 99, no. 16, pp. 963-970.

van Kuijk, A.A., Anker, L.C., Pasman, J.W., Hendriks, J.C.M., van Elswijk, G. and Geurts, A.C.H. (2009) "Stimulus–response characteristics of motor evoked potentials and silent periods in proximal and distal upper-extremity muscles", *Journal of Electromyography and Kinesiology,* vol. 19, no. 4, pp. 574-583.

van Tuijl, J.H., Janssen-Potten, Y.J. and Seelen, H.A. (2002) "Evaluation of upper extremity motor function tests in tetraplegics", *Spinal cord : the official journal of the International Medical Society of Paraplegia,* vol. 40, no. 2, pp. 51-64.

Vaughan, J., Barany, D.A., Sali, A.W., Jax, S.A. and Rosenbaum, D.A. (2010) "Extending Fitts' Law to three-dimensional obstacle-avoidance movements: Support for the posture-based motion planning model", *Experimental Brain Research,* vol. 207, no. 1-2, pp. 133-138.

Vavrek, R., Girgis, J., Tetzlaff, W., Hiebert, G.W. and Fouad, K. (2006) "BDNF promotes connections of corticospinal neurons onto spared descending interneurons in spinal cord injured rats", *Brain : a journal of neurology,* vol. 129, no. Pt 6, pp. 1534-1545.

Vidoni, E.D., Acerra, N.E., Dao, E., Meehan, S.K. and Boyd, L.A. (2010) "Role of the primary somatosensory cortex in motor learning: An rTMS study", *Neurobiology of learning and memory,* vol. 93, no. 4, pp. 532-539.

Vines, B.W., Cerruti, C. and Schlaug, G. (2008) "Dual-hemisphere tDCS facilitates greater improvements for healthy subjects' non-dominant hand compared to uni-hemisphere stimulation", *BMC neuroscience,* vol. 9, pp. 103.

Vogt, S., Buccino, G., Wohlschläger, A.M., Canessa, N., Shah, N.J., Zilles, K., Eickhoff, S.B., Freund, H., Rizzolatti, G. and Fink, G.R. (2007) "Prefrontal involvement in imitation learning of hand actions: Effects of practice and expertise", *NeuroImage,* vol. 37, no. 4, pp. 1371-1383.

Walsh, B., Howlett, R.A., Stary, C.M., Kindig, C.A. and Hogan, M.C. (2006) "Measurement of activation energy and oxidative phosphorylation onset kinetics in isolated muscle fibers in the absence of cross-bridge cycling", *American Journal of Physiology - Regulatory Integrative and Comparative Physiology,* vol. 290, no. 6, pp. R1707-R1713.

Wang, W., Chan, S.S., Heldman, D.A. and Moran, D.W. (2010) "Motor cortical representation of hand translation and rotation during reaching", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 30, no. 3, pp. 958-962.

Warraich, Z. and Kleim, J.A. (2010) "Neural plasticity: the biological substrate for neurorehabilitation", *PM & R : the journal of injury, function, and rehabilitation,* vol. 2, no. 12 Suppl 2, pp. S208-19.

Wass, T.S., Simmons, R.W., Thomas, J.D. and Riley, E.P. (2002) "Timing accuracy and variability in children with prenatal exposure to alcohol", *Alcoholism: Clinical and Experimental Research,* vol. 26, no. 12, pp. 1887-1896.

Wassermann, E.M. (1998) "Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996", *Electroencephalography and Clinical Neurophysiology - Evoked Potentials,* vol. 108, no. 1, pp. 1-16.

Wassermann, E.M., McShane, L.M., Hallett, M. and Cohen, L.G. (1992) "Noninvasive mapping of muscle representations in human motor cortex", *Electroencephalography and clinical neurophysiology,* vol. 85, no. 1, pp. 1-8.

Webster, B.R., Celnik, P.A. and Cohen, L.G. (2006) "Noninvasive Brain Stimulation in Stroke Rehabilitation", *NeuroRx,* vol. 3, no. 4, pp. 474-481.

Williams, J.A., Imamura, M. and Fregni, F. (2009) "Updates on the use of non-invasive brain stimulation in physical and rehabilitation medicine.", *Journal of rehabilitation medicine : official journal of the UEMS European Board of Physical and Rehabilitation Medicine,* vol. 41, no. 5, pp. 305-311.

Wilson, P.H., Maruff, P., Ives, S. and Currie, J. (2001) "Abnormalities of motor and praxis imagery in children with DCD", *Human Movement Science,* vol. 20, no. 1-2, pp. 135-159.

Wilson, S.A., Thickbroom, G.W. and Mastaglia, F.L. (1995) "Comparison of the magnetically mapped corticomotor representation of a muscle at rest and during low-level voluntary contraction", *Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control,* vol. 97, no. 5, pp. 246-250.

Winges, S.A., Weber, D.J. and Santello, M. (2003) "The role of vision on hand preshaping during reach to grasp", *Experimental Brain Research,* vol. 152, no. 4, pp. 489-498.

Witney, A.G., Vetter, P. and Wolpert, D.M. (2001) "The influence of previous experience on predictive motor control", *Neuroreport,* vol. 12, no. 4, pp. 649-653.

Wittenberg, G.F. (2010) "Experience, cortical remapping, and recovery in brain disease", *Neurobiology of disease,* vol. 37, no. 2, pp. 252-258.

Wong, Y.J. and Whishaw, I.Q. (2004) "Precision grasps of children and young and old adults: individual differences in digit contact strategy, purchase pattern, and digit posture", *Behavioural brain research,* vol. 154, no. 1, pp. 113-123.

Worringham, C.J. (1991) "Variability effects on the internal structure of rapid aiming movements", *Journal of motor behavior,* vol. 23, no. 1, pp. 75-85.

Wrigley, P.J., Gustin, S.M., Macey, P.M., Nash, P.G., Gandevia, S.C., Macefield, V.G., Siddall, P.J. and Henderson, L.A. (2009) "Anatomical changes in human motor cortex and motor pathways following complete thoracic spinal cord injury", *Cerebral cortex (New York, N.Y.: 1991),* vol. 19, no. 1, pp. 224-232.

Wyndaele, M. and Wyndaele, J.J. (2006) "Incidence, prevalence and epidemiology of spinal cord injury: what learns a worldwide literature survey?", *Spinal cord : the official journal of the International Medical Society of Paraplegia,* vol. 44, no. 9, pp. 523-529.

Yamada, K. and Nabeshima, T. (2004) "Interaction of BDNF/TrkB signaling with NMDA receptor in learning and memory", *Drug news & perspectives,* vol. 17, no. 7, pp. 435-438.

Yan, Q., Rosenfeld, R.D., Matheson, C.R., Hawkins, N., Lopez, O.T., Bennett, L. and Welcher, A.A. (1997) "Expression of brain-derived neurotrophic factor protein in the adult rat central nervous system", *Neuroscience,* vol. 78, no. 2, pp. 431-448.

Yancosek, K.E. and Howell, D. (2009) "A narrative review of dexterity assessments", *Journal of hand therapy : official journal of the American Society of Hand Therapists,* vol. 22, no. 3, pp. 258-269.

Yarrow, K., Brown, P. and Krakauer, J.W. (2009) "Inside the brain of an elite athlete: The neural processes that support high achievement in sports", *Nature Reviews Neuroscience,* vol. 10, no. 8, pp. 585-596.

Zanette, G., Bonato, C., Polo, A., Tinazzi, M., Manganotti, P. and Fiaschi, A. (1995) "Long-lasting depression of motor-evoked potentials to transcranial magnetic stimulation following exercise", *Experimental brain research.,* vol. 107, no. 1, pp. 80-86.

Zariffa, J., Kapadia, N., Kramer, J.L.K., Taylor, P., Alizadeh-Meghrazi, M., Zivanovic, V., Willms, R., Townson, A., Curt, A., Popovic, M.R. and Steeves, J.D. (2012) "Feasibility and efficacy of upper limb robotic rehabilitation in a subacute cervical spinal cord injury population", *Spinal Cord,* vol. 50, no. 3, pp. 220-226.

Ziemann, U., Corwell, B. and Cohen, L.G. (1998) "Modulation of plasticity in human motor cortex after forearm ischemic nerve block", *The Journal of neuroscience : the official journal of the Society for Neuroscience,* vol. 18, no. 3, pp. 1115-1123.

Ziemann, U., Lonnecker, S., Steinhoff, B.J. and Paulus, W. (1996) "Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study", *Annals of Neurology,* vol. 40, no. 3, pp. 367-378.

Ziemann, U., Muellbacher, W., Hallett, M. and Cohen, L.G. (2001) "Modulation of practice-dependent plasticity in human motor cortex", *Brain : a journal of neurology,* vol. 124, no. Pt 6, pp. 1171-1181.

Appendices

Appendix A. CX-6650 DC stimulator unit datasheet.

Rolf Schneider electronics

DC-Stimulator CX-6650 Model TRCU-03 E

Size : 220 x 95 x 250 mm without handle, 252 x 95 x 270 mm with handle

Output range: 0,1 µA ... 10 mA
(5 decimal ranges, selectable by range selector switch and variable adjustment)

Timer control: 1min ... 40 min (in 1-minute-steps or continuous)
Arbitrary stimulation times or interruption of the actual timer-cycle
can be accomplished manually or externally by trigger signal via optically isolated control input.

Linear current increase at the beginning of stimulation up to the level set by the current controls
and linear decrease down to zero at the end of stimulation
adjuastable from 0,05 to 10 sec (0,3 to 10 sec in the lowest current range).
Ramp mode is indicated by flashing 'active' – indicator lamp.

Acoustic indicator for start and end of stimulation (high tone, low tone). Volume control on rear panel.

Direct measurement and digital display of output current and voltage.

Ranges and units of the current panel meter are switched by the current range selector
for optimum resolution of the digital readout in every current range.

A protection circuit supervises the delivered voltage and current to the electrodes
and switches off the output in case of a failure of the control electronics.

Single user friendly toggle mode Start/Stop push button.

LED – indicators for Standby, Activated Output, Excess of Voltage Compliance Range,
Low Batteries and of the Protection Circuit Activation.

Power supply: 4 standard size (AA) rechargeable NiMH cells 1,2V / 2300mAh.
A second set (4 cells) is included for fast exchange of discharged to recharged units.

The instrument is constructed for use under normal environmental conditions.

November 2004

Appendix B. Administration instructions for the Motor Skill Rehabilitation Task (MSRT)

Refer to MSRT task illustration Figure 2.2.

Preparation and instructions to participants

The board is placed on a desk table with the front of the board aligned with the edge of the table and the midline of the board aligned with the centre of the left shoulder joint (acromion process). If necessary adjust the height of the participant so that, with the body in a comfortable sitting position and the shoulder neutrally aligned, the acromion process of the elbow is aligned approximately level with the table top. Ensure that the start/stop button, peg tray and rail array are easily accessible to the participants. The participant selects 5 pegs from a selection and places them in the dish tray.

The investigator sits to the right of the participant, close enough to reach the rail board and with a computer to the front running the stopwatch timer function. A team of investigators may share these administration tasks.

The examiner explains the task activity as follows, indicating each component of the apparatus:

"This task is designed to be carried out using your left arm and hand only. Please keep your right arm and hand clear of the board."

"These are the 5 rails mounted towards the back of the board, which as you can see are placed at different angles and are numbered 1 to 5. ***(Indicate).***

"This is the peg dish and these are the pegs. All of the pegs are the same."

"This is the stopwatch button. Press this button to begin and end each trial. The button operates a stopwatch function on the computer" ***(indicate the red button).***

"Once you have pressed the button with your *left hand* to start the task, as quickly as you can pick up a single peg and, starting with the leftmost rail 1 and working to the right, place it in the groove across both the raised supports ***(investigator demonstrates)***. "Then pick up a further peg from the tray; place it across the next rail along and so on without skipping any, *from left to right* in the order 1 2 3 4 5 until all the pegs are placed on all the rails." (***The***

investigator should demonstrate a full trial, making clear that the pegs are to be placed from subject's left to right in the correct order and using the left hand only).

"If you drop a peg or make a mistake during a rail attempt, for example at number 2 then leave that rail empty. You have one attempt only at each rail. Don't attempt to correct any errors as you will lose time in completing the task. Pick up a new peg from the dish and move on to the next rail (in this example, number 3). As soon as you place the last peg, press the button again with your *left hand* to end the task." ***(Demonstrate).***

"It will take a few seconds for me to reset the task. Once it is reset, I will say "Ready" and you can then begin the task again when you feel ready. Once you have completed the task *N* times we can have a short rest".

"Always try and complete the task as quickly and accurately/accurately and quickly as you can."

Start when you are ready, by pressing the timer button."

Give each participant at least 1 practise trial before commencing data collection. This is to ensure that a) he/she understands the sequential activity; b) that during 'live' trials, the pegs have been replaced in the dish only by tilting the rail board, so ensuring that pegs fall into a semi-randomised pattern. Discourage participants from interfering with peg arrangements in the tray as this could bias the difficulty of the task.

During task trials

Make sure the stopwatch has been triggered at the start of the trial

Watch out for 'dependent' errors. The design of the rails generally results in correctly placed pegs remaining secure once released. If a peg is inadvertently dislodged later in the trial, by vibration or by contact with the moving upper limb for example, this should not be marked as an error.

Scoring

Task completion time: The start/end button is linked to a computer-based stopwatch function and automatically records the task completion time. This is tabulated in Excel for later analysis.

Error is recorded on a Session Proforma sheet each time the participant fails to correctly place a peg: either by dropping the peg, placing the peg so that it rests on one support only or placing the peg insecurely so that it immediately falls.

Error may be recorded in successive Motor Error Log trial boxes either as a numeral representing the number of errors per trial, or as dots representing the location of the error as per the task layout. This allows for more in-depth analysis of task parameters over time.

Resetting the task

Once a task trial has been completed, carry out the following operations:

1. Zero the stopwatch
2. ***Always record the position of ERRORS on the spatial error log form***. Even though the TPR outcome measure is calculated from (time/number of accurate placements) formula you will find it easier to record error position as these are usually less frequent than accurate placements!
3. Reach across and tilt the rail board up smartly, in order to release the pegs back into the blue peg dish.

Appendix C. MSRT generic error log sheet

Motor task error log

Study title:

Participant Number **Date** **Time**

MSRT Rotation layout

Block Trial	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
1										
2										
3										
4										
5										
6										
7										
8										
9										
0										

Appendix D. Ethical approvals

Explanatory note

Ethical approvals were separately sought and granted for all research studies. Studies 1and 3 were carried out on the Brunel University campus, involved healthy staff and/or students and so required a single stage ethical approval from the School of Health Sciences and Social Care Research Ethics Committee (REC). Study 2 was carried out on a NHS hospital site and involved NHS patients. For this study, additional approvals were sought from, and granted by NHS Local RECs and the NHS site Research and Development Department.

Study 1

Brunel
UNIVERSITY
WEST LONDON

School of Health Sciences and
Social Care

Research Ethics Committee

School of Health Sciences and
Social Care
Brunel University,
Uxbridge
Middlesex UB8 3PH
Telephone: +44 (0)1895 274000
Web www.brunel.ac.uk

15 February 2011

Approval of Amendment to Protocol

Proposer: **James Ashworth-Beaumont**

Title: **Revised Research Ethics Application – Study title 'Investigating the properties of a novel upper limb motor skill rehabilitation task'.**

Reference: **11/11/PHD/07**

The School Research Ethics Committee has considered the amendment to protocol submitted by you on 3rd February 2011 with regard to the above study. Acting under delegated authority, the Chair is satisfied that there is no objection on ethical grounds to the amendment. Approval is given on the understanding that the conditions of approval set out below are followed:

- *The agreed protocol must be followed. Any changes to the protocol will require prior approval from the Committee.*

NB:

- **Research participant information sheets and (where relevant) flyers, posters and consent forms, should include a clear statement that research ethics approval has been obtained from the School of Health Sciences and Social Care Research Ethics Committee.**
- **Approval to proceed with the study is granted subject to receipt by the Committee of satisfactory responses to any conditions that may appear above, in addition to any subsequent changes to the protocol.**

David Anderson-Ford
School Research Ethics Officer
School of Health Sciences and Social Care

Study 2

Brunel UNIVERSITY WEST LONDON

School of Health Sciences and Social Care

Research Ethics Committee

School of Health Sciences and Social Care
Brunel University,
Uxbridge
Middlesex UB8 3PH
Telephone: +44 (0)1895 274000
Web www.brunel.ac.uk

15 March2010

Proposer: **James Ashworth-Beaumont PhD Student**

Title: **Effects of anodal tDCS on skill learning in relation to the non-dominant upper limb of incomplete cervical spinal cord injured subjects: a pilot study**

Reference: **09/12/PHD/05**

Letter of Approval

The School Research Ethics Committee has considered the amendments recently submitted by you in response to the Committee's earlier review of the above application

The Chair, acting under delegated authority, is satisfied that the amendments accord with the decision of the Committee and has agreed that there is no objection on ethical grounds to the proposed study. Approval is given on the understanding that the conditions of approval set out below are followed:

- *The agreed protocol must be followed. Any changes to the protocol will require prior approval from the Committee.*

NB:

- **Research Participant Information Sheets and (where relevant) flyers, posters, and consent forms should include a clear statement that research ethics approval has been obtained from the School of Health Sciences and Social Care Research Ethics Committee.**
- **The Research Participant Information Sheets should include a clear statement that queries should be directed, in the first instance, to the Supervisor (where relevant), or the researcher. Complaints, on the other hand, should be directed, in the first instance, to the Chair of the School Research Ethics Committee**
- **Approval to proceed with the study is granted subject to receipt by the Committee of satisfactory responses to any conditions that may appear above, in addition to any subsequent changes to the protocol.**
- **The School Research Ethics Committee reserves the right to sample and review documentation, including raw data, relevant to the study.**

David Anderson-Ford
Chair, Brunel University Research Ethics Committee
School Research Ethics Officer
School of Health Sciences and Social Care

Royal National Orthopaedic Hospital NHS
NHS Trust

R&D Office
% UCL-IOMS
RNOH, Brockley Hill
Stanmore HA7 4LP
Tel: 020 8909 5529
Fax: 020 8909 5273
E-mail: iva.hauptmannova@moh.nhs.uk

NHS R&D Management Approval Letter for Research

To: Mr James Ashworth-Beaumont

From: Iva Hauptmannova (R&D manager)

Date: 2nd of June 2010

Project Title: Effects of anodal transcranial direct current stimulation (tDCS) on skill learning in relation to the non-dominant upper limb of incomplete cervical spinal cord injured subjects: a pilot study

REC Ref: **10/H0724/24**

R&D Ref: **10.008**

Sponsor: **Brunel University**

I understand that you have received a favourable ethics opinion for the above project, with the condition that you do not undertake research in an NHS organisation until relevant NHS Management Approval has been received. I am therefore writing on behalf of the Royal National Orthopaedic Hospital NHS Trust Stanmore, to inform you that the project has been approved by the Trust and may now proceed.

To maintain this approval, the following conditions must be met:

1. All staff involved in the running of this study must adhere to Trust and Research Governance Framework requirements.

2. As Chief/Principal Investigator you are required to formally advise the R&D Office of **ANY** changes to the project including:
   - Any changes to the status of the project, e.g. abandoned, completed etc
   - Any changes to the protocol – however minor.
   - Any changes to the funding arrangements.

3. The Chief/Principal Investigator is also required to:
   - Notify the R&D, in a timely fashion, any Serious Adverse Events relating to the Research and the appropriate urgent safety measures taken in line with ICH GCP requirements.

- Ensure that the R&D Office has copies of all annual and final progress reports.
- Ensure all researchers involved in the project hold the necessary expertise required and have Honorary Contracts should they need to.
- Ensure adequate and accurate reporting and monitoring of said project.
- Co-operate with all internal Trust monitoring and auditing procedures.

4. Because it is a statutory requirement to submit annual reports, this approval will automatically lapse if no annual report on this study is received at the R&D office, 14 months from the date of this letter. If you need help on how to prepare your annual report, please contact the R&D Office at the address on this letter.

Yours sincerely,

Iva Hauptmannova
R&D Manager

NHS

National Research Ethics Service

North London REC 2
Northwick Park Hospital
Room 019, Level 7 Maternity Block
Watford Road
Harrow
Middlesex
HA1 3UJ

Telephone: 020 8869 3020
Facsimile: 020 8869 5222

27 May 2010

Mr James Ashworth-Beaumont
Post-Graduate Researcher
Brunel University of West London
Mary Seacole Building, Brunel Uni
Kingston Lane, Uxbridge
Middx
UB8 3PH

Dear Mr Ashworth-Beaumont

Study Title:	**Effects of anodal transcranial direct current stimulation (tDCS) on skill learning in relation to the non-dominant upper limb of incomplete cervical spinal cord injured subjects: a pilot study**
REC reference number:	**10/H0724/24**
Protocol number:	**n/a**

Thank you for your letter of 17th May 2010 responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee me (Committee Chair).

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm **a favourable ethical opinion** for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Questionnaire: Health Questionnaire	d	
Questionnaire: Primary Health Questionnaire	a	

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

10/H0724/24	**Please quote this number on all correspondence**

Yours sincerely

pp Chaudhry

Mrs Rosemary Hill
Chair

Email: uzma.chaudhry@nwlh.nhs.uk

Enclosures: "After ethical review – guidance for researchers"

Copy to:

Dr Alexander Nowicky
Mary Seacole Building
Kingston Lane
Uxbridge
Middx UB8 3PH

Study 3

Brunel UNIVERSITY LONDON

School of Health Sciences and Social Care

Research Ethics Committee

School of Health Sciences and Social Care
Brunel University,
Uxbridge
Middlesex UB8 3PH
Telephone: +44 (0)1895 274000
Web www.brunel.ac.uk

29th June 2011

Proposer: James Ashworth-Beaumont

Title: The lasting effect of adjunctive tDCS on non-dominant skill learning and associated cortical excitability in healthy adults

Reference: 11/06/PHD/09

Letter of Approval

The School Research Ethics Committee has considered the proposal recently submitted by you. Acting under delegated authority, the Chair is satisfied that there is no objection on ethical grounds to the proposed study. Approval is given on the understanding that the conditions of approval set out below are followed:

- *The agreed protocol must be followed. Any changes to the protocol will require prior approval from the Committee.*

NB:

- **Research participant information sheets and (where relevant) flyers, posters and consent forms, should include a clear statement that research ethics approval has been obtained from the School of Health Sciences and Social Care Research Ethics Committee.**
- **The Research Participant Information Sheets should include a clear statement that queries should be directed, in the first instance, to the Supervisor (where relevant), or the researcher. Complaints, on the other hand, should be directed, in the first instance, to the Chair of the School Research Ethics Committee**
- **Approval to proceed with the study is granted subject to receipt by the Committee of satisfactory responses to any conditions that may appear above, in addition to any subsequent changes to the protocol.**

David Anderson-Ford
School Research Ethics Officer
School of Health Sciences and Social Care

Appendix E. Assessment, health screening and consent proforma

Explanatory note

Study 2 involved the recruitment and characterisation of incomplete tetraplegic SCI patients and additional proforma are presented as follows. In some cases these are exemplars of proforma used in other studies, as indicated.

- Invitation letter
- Participant information sheet *
- Pilot study participant assessment checklist
- Edinburgh handedness inventory (modified) ‡
- GPCOG Screening Test (step 1)
- ASIA impairment scale classification format
- Pilot study health questionnaire
- Consent form
- Subjectives questionnaire#

* Exemplar of participant information sheet format adopted for all studies.
‡ Adopted for assessment, studies 1, 3 and 4.
# Adopted for studies 3 and 4.

Brunel
UNIVERSITY
WEST LONDON
School of Health Sciences and Social Care
Brunel University,
Uxbridge
Middlesex UB8 3PH
Telephone: +44 (0)1895 274000
Web www.brunel.ac.uk

Study 1

Health Screening and Consent Form

Study title: Investigating the properties of a novel upper limb motor skill rehabilitation task

This study has been approved by the School of Health Sciences and Social Care Research Ethics Committee

General Health Screening Questionnaire

Subject: **Gender:** **Age:** **Date:**

Confidential

Please answer the following health related questions.

If you answer yes to any of these questions then you should not participate in the study.

Please circle your responses

Question	**Response**
I feel unwell today.	Yes No
I suffer from dizziness.	Yes No
I suffer from balance disturbances.	Yes No
I have a problem affecting the movement of my arms or hands	Yes No
I have had a neurosurgical procedure (operation to the skull).	Yes No
I have a neurological condition (including epilepsy).	Yes No
I have an severe, uncorrected visual impairment	Yes No

If you have answered "no" to all of the above questions then you may participate in the research using these techniques. Your participation is entirely voluntary. You may

withdraw at any time from any session for any or no reason. Should you choose not to participate or to withdraw from a session, your status as a student or staff of Brunel University will in no way be affected.

If at any time during the session you wish to take a rest, or withdraw your consent to continue, inform the investigator verbally: the procedure will be paused or stopped immediately.

If you have any concerns please feel free to ask for further information.

Risk and Discomfort

Brunel University's health and safety practices are observed in our laboratory and participant safety is of paramount importance at all times.

During this study we will ask you to undertake a simple training task and carry out several validated tests of upper limb performance. All motor task and measurement procedures are entirely non-intrusive and safe to apply healthy adults. No hazards have been detected in relation to appropriately supervised study activity and no side-effects of participation are expected to arise over any time frame.

Prior to commencement, participants will be asked to complete the above questionnaire and if any answers are positive they will be excluded from the study. All participants will be asked to sign the consent form. In the case of reported discomfort or mild headache the procedure will be stopped and the participant will be withdrawn from the study.

Part 2: Consent Form

Study Title: Validation of a new motor skill rehabilitation task

Brunel UNIVERSITY WEST LONDON
School of Health Sciences and Social Care
Brunel University,
Uxbridge
Middlesex UB8 3PH
Telephone: +44 (0)1895 274000
Web www.brunel.ac.uk

Chief Investigator: Jim Ashworth-Beaumont

James.ashworth-beaumont@brunel.ac.uk

Tel: 07723 053199

Consent Form – Archive Copy

Please read this form carefully. Please voice any questions or concerns you may have. Remember that you are free to withdraw your consent at any time before or during the session. Please indicate your agreement to each statement by *initialing the corresponding box.*

1. I have had the opportunity to ask questions and my questions have been answered to my satisfaction	
2. I understand that my participation in this study is entirely voluntary.	
3. I understand that I am free to withdraw my consent to take part, before of during participation in this study at any time without giving any reason, without my current or future status as a member of staff or student being detrimentally affected in any way.	
4. I understand that my identity will not be referred to or revealed in any published documentation arising from this study.	
5. I agree to the anonymised data arising from this study being stored beyond the completion date, for use in further research and educational studies.	

I understand the information contained in the Research Participant Information Sheet and this Consent Form. I give my consent to participate in this study.

_____ _____ _____

Name of participant Date Signature

_____ _____ _____

Name of person taking consent Date Signature

A duplicate copy was provided to the participant.

Study 2

Invitation letter

Brunel
UNIVERSITY
WEST LONDON
School of Health Sciences and Social Care
Brunel University,
Uxbridge
Middlesex UB8 3PH
Telephone: +44 (0)1895 274000
Web www.brunel.ac.uk

Dear

I am a Post-graduate Researcher studying for a PhD in Health Studies at Brunel University. I am currently planning an experimental study which is running at the Mary Seacole Building, Brunel University and which will be open to participants until the end of June 2011. The aim of this study is to investigate the effect of a novel intervention; anodal transcranial direct current stimulation (tDCS) which previous research indicates may help to enhance the rehabilitation of upper limb function in incomplete spinal cord injured persons.

In order to carry out this scientific study properly, we need to include a group of people who are similar in a number of ways. You are being invited to participate because your medical history, based on the records of the Spinal Cord Injury Centre, RNOH indicates that you may be suitable. If the following *inclusion criteria* apply to you, you may be able to take place in this study:

Inclusion criteria
• You are a man or woman, aged 18 to 70 years inclusive; • The spinal cord injury happened more than 12 months ago; • This injury is incomplete and classified C or D, at ASIA level C5, C6 or C7; • you were right-hand dominant prior to your spinal injury; • You are able, *using the left hand only*, to pick up a small, light object (such as a pen top) from a table surface; • Your medical condition is stable

although we regret that if the following *exclusion criteria* apply to you, we will be unable to invite you to take part in this study:

Exclusion critera
• You have a severe, uncorrected visual impairment; • You have previously suffered a head injury or seizures or had surgery to the head; • You have a currently unstable medical condition and/or are symptomatic for autonomic dysreflexia ; • You have previously had surgery to the left hand to improve its function; • You are pregnant

If you think you will be eligible, and able to take part in this study at any time between now and the 30th of June 2011, please read through the Participant Information Sheet included with this letter. This document provides full details of the study including the purpose, duration, potential risks and benefits to you. The study has been reviewed and approved on ethical grounds in accordance with the Declaration of Helsinki, by the Research Ethics Committees of the School of Health Sciences and Social Care, Brunel University and the NHS North London Research Ethics Committees 2 and 3.

Please be assured that you are under no obligation to participate. If you do consent to take part in the study, you may withdraw at any time without any negative consequences. Your status as a patient would not be affected in any way. In any event, your confidentiality will be respected at all time.

If you wish to part in this study, or simply have a question please do not hesitate to contact me by telephone, e-mail or post. My contact details can be found below.

Alternatively you may wish to contact the Academic Supervisor for this study, Dr Alexander Nowicky, by telephone on *0189 526 8813, by e-mail at* alexander.nowicky@brunel.ac.uk or by post at the above address.

Yours sincerely,
James Ashworth-Beaumont,

Post-graduate Researcher,
School of Health Sciences and Social Care,
Brunel University of West London,
Kingston Lane,
Uxbridge,
Middlesex UB8 3PH
Tel: 07723 053199
E-mail: James.ashworth-beaumont@brunel.ac.uk

Royal National Orthopaedic Hospital NHS
NHS Trust

RNOH Stanmore
Brockley Hill
Stanmore
Middlesex
HA7 4LP
Tel: 020 8954 2300
www.rnoh.nhs.uk

PARTICIPANT INFORMATION SHEET

Study title

Effects of anodal transcranial direct current stimulation (tDCS) on skill learning, in relation to the non-dominant upper limb of incomplete cervical spinal cord injured subjects: a pilot study

Invitation paragraph

We would like to invite you to take part in this research study. Before you decide whether to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Part 1 tells you the purpose of this study and what will happen to you if you decide to take part. Part 2 gives you more detailed information about how the study will be carried out.

Information sheet part 1

What is the purpose of the study?

This is a pilot study forming part of a PhD project.

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique. Previous experimental studies have demonstrated the potential of this safe and painless technique, when applied during the learning of motor skills, to induce significant changes in brain excitability, improving learning effects and skill performance.

The aim of the present project is to explore the extent of benefit to functionally incomplete cervical spinal cord injured (SCI) participants in improving functioning of the left hand. We

hope to establish whether tDCS might enhance function both over the short term and in a lasting fashion.

What is Transcranial Direct Current Stimulation (tDCS)?

tDCS is a simple and painless technique where electrode pads are dampened with a mild salt water solution, then arranged onto specific areas of the head and gently held in place with straps (fig 1). You will need to wear the electrodes during each of the 3 training sessions. This will not impair your vision or hearing in any way. There is no restriction on hair length or style, although the straps and pads will tend to flatten the hair to the head.

The electrode pads will be connected to a battery-driven electrical stimulator (fig 2). A small current is then passed between the electrodes to temporarily alter the activity of the underlying areas of the brain. This sometimes causes mild sensations underneath the electrode pads for a few seconds, as the stimulator is switched on or off.

Why have I been invited?

You have been invited because we think you fit the initial inclusion criteria of this study. Two groups, each of up to 12 individuals will participate in this study. People that *do not* meet the inclusion criteria, or to whom the exclusion criteria apply, will not be included in the study. The inclusion and exclusion criteria are summarised in the tables below.

Inclusion criteria
• You are a man or woman, aged 18 to 70 years inclusive; • The spinal cord injury happened more than 12 months ago; • This injury is incomplete and classified C or D, at ASIA level C5, C6 or C7; • you were right-hand dominant prior to your spinal injury; • You are able, using the left hand only, to pick up a small, light object (such as a pen top) from a table surface; • Your medical condition is stable

Exclusion critera
• You have a severe, uncorrected visual impairment; • You have previously suffered a head injury or seizures or had surgery to the head; • You have a currently unstable medical condition and/or are symptomatic for autonomic dysreflexia; • You have previously had surgery to the left hand to improve its function. • You are pregnant

Do I have to take part?

It is entirely up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your status as a patient in any way.

What is involved in the study?

All study activities will take place at the London Spinal Cord Injury Centre, The Royal National Orthopaedic Hospital NHS Trust, Brockley Hill, Stanmore, Middx HA7 4LP.

If you wish to take part in this study you will be invited to take part in a preliminary screening and briefing session at the study site. Those participants who pass the screening process will, over several days undergo training in a skill task specially designed to challenge dexterity of grip in the left hand. During part of each session, either active or placebo stimulation will be applied to the head. Immediately before and after each skill session, participants will be asked to carry out some brief manual tests to give us information we can use to determine the extent of changes in functional performance over time.

The study does not require any dietary or life style restrictions. If you are a wheelchair user or have special seating requirements, please bring these with you as all training and testing will take place in a seated position.

Length of the study and what will happen

First we require you to attend a preliminary Assessment session, either a few days before the study proper begins, *or on the same day as the study begins if this is more convenient for you*. The aims of this session are firstly to carry out some further assessment and screening to ensure you are suitable for inclusion. Secondly, during this session we can demonstrate the activities taking place during the study, to further help you decide whether you still wish to take part. The Assessment Session will take a maximum of 60 minutes to complete. Attendance at the Assessment session does not commit you in any way to taking part in the study.

The study itself will take place over 3 consecutive days, with a follow-up session 5-7 days after that. All these sessions are important in order to determine whether the effects of tDCS are cumulative and whether the effects are lasting.

Each session and the follow-up session will consist of the following activities:

10 minutes[†]:	Complete health questionnaire and provide consent;
5 minutes:	Prepare tDCS equipment;
12 minutes:	Functional testing;
45 minutes*****:	Skill training, during which active or sham/placebo tDCS is applied;
5 minutes:	Remove tDCS equipment;
12 minutes:	Functional testing;
5 minutes:	Subjective questionnaire.

([†] The study consent form will also be signed during the first session; ***** During the follow-up session, task training will be for a shorter period of time and tDCS will not be applied).

We expect each session to last a maximum of 1 hour and 45 minutes.

Research methods

Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each individual is allocated to a group.

In the present study you will have an equal 50/50 chance of receiving the active brain stimulation or a sham substitute.

This is a 'blinded trial' study. This means that you will not know in which treatment group you are (although, if your doctor needs to find out he/she can do so).

Expenses and payments

Our funds are very limited, and so in general we are only able to offer modest reimbursement of travel expenses up to a maximum of £30 per participant. Any reimbursement will be payable after the study is finished.

What are the possible risks or side effects?

The evidence from previous studies is that many participants do not feel any effects of tDCS. Some people have reported slight itching, tingling and burning sensation under the electrodes during and after stimulation. The reported incidence is very low, with any effects being short-lasting. Rare occurrences of minor skin burns under electrodes have been reported and have resulted in no permanent harm to participants. These effects have only occurred when established application procedures have not been followed.

What are the side-effects of the treatment?

The level of tDCS intensity, the number of and period between stimulation sessions to be used in the present study is well within the limits established as safe in numerous studies.

The itching, tingling or burning sensations which some people experience during the procedure are mild and short-lasting. No long-lasting adverse effect of anodal tDCS has ever been reported, in the configurations to be used in the present study.

What are the possible benefits of taking part?

We cannot promise that the study will help you.

We are investigating weak direct current brain stimulation (tDCS) as a potentially beneficial intervention, but we may find that applying this intervention reduces, or has no effect on upper limb function.

But the information we get will be of great importance: it will give us more insight to how tDCS affects the human brain while evoking functional changes when applied in conjunction with manual rehabilitation techniques. This knowledge will be invaluable in designing the protocols for future studies and interventions for SCI clients. The outcomes of this study will also inform future rehabilitation techniques for the wider population of individuals affected by neurological disorders.

What happens when the research stops?

We must make it clear that tDCS remains an experimental intervention at this time, so will not be available as a treatment after the study is completed.

What if there is a problem?

Any complaint about the way you have been dealt with during the study, or any possible discomfort you might feel, will be addressed. Detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Information sheet part 2

What if relevant new information becomes available?

Sometimes, during the course of a research project, new information becomes available about the intervention that is being studied. If this happens, the researchers will tell you about it and discuss whether or not you want to continue in the study. If you decide not to carry on, your status as a patient/client will not be affected in any way. If you decide to continue in the study, you will be asked to sign an updated consent form.

What will happen if I don't want to carry on with the study?

Your participation in this trial is entirely voluntary. You are free to decline to enter or to withdraw from the study any time without having to give a reason. If you choose not to enter the trial, or to withdraw once entered, this will in no way affect your future status as a patient/client.

What if I am unable to complete the study?

In the event that once enrolled you are unable to complete the study or take part in one or more of the sessions, we would still like to include any information collected to help analyse the study outcomes. You are free to withdraw consent for us to do so, without affecting your future status as a patient/client.

What if there is a problem?

Complaints

If you have a concern about any aspect of this study, feel free to speak with the researchers who will do their best to answer all of your questions. If you remain unhappy and wish to complain more formally, you can do this by contacting the academic supervisor of this study. The contact numbers are at the end of this information sheet.

You may also complain formally by contacting the Project Sponsor via:

David Anderson-Ford,

Chair of the University Research Ethics Committee,
Mary Seacole Building,
Brunel University of West London,
UXBRIDGE, Middx UB8 3PH
Tel: 01895 268731

Alternatively, you may wish to lodge a complaint using the NHS Trust Complaints Procedure via:

The Customer Care Manager,

Royal National Orthopaedic Hospital NHS Trust,
Brockley Hill, Stanmore,
Middlesex, HA7 4LP

Tel: 020 8909 5717

Email: customercare@rnoh.nhs.uk

Harm

In the unlikely event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation, but you may have to pay your legal costs.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be secured and kept strictly confidential. Any information about you which leaves the study facility at The Royal National Orthopaedic Hospital NHS Trust, Stanmore Site will have your name and address, date of birth and all identifiable information removed so that you cannot be identified from it. All information regarding your personal details will be treated as strictly confidential, will only be used for audit purposes and will be destroyed after 6 months. The trial results may be inspected by competent authorities and properly authorised persons, but if any information is released this will be done in a coded form so that confidentiality is strictly maintained.

For 5 years after the conclusion of the study, the anonymised data will be secured at Brunel University, West London under the custodianship of the Academic Supervisor.

Involvement of the Family Doctor (GP)

In the best interests of your health it is important that your doctor is aware of any therapeutic intervention you are having, even though your standard treatment may not be affected. We will ask you to provide consent for us to write a brief letter explaining your inclusion in the study. No other information personal to you will be exchanged.

What will happen to the results of the research study?

The results of this study will be included as part of a PhD Thesis. Additionally, it is intended to present the findings for peer review. On completion of the study, an abstract summarising the study findings will be sent to you. You will not be identified in any report/publication.

Who is organising and funding the research?

The research is organised and funded by the School of Health Sciences and Social Care, Brunel University. No conflicts of interest, financial or otherwise exist with respect to the study researchers or collaborating organisations.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by the NHS North London Research Ethics Committee 2.

Contacts for further information

For further information, please do not hesitate to contact:

Project Researcher: Jim Ashworth-Beaumont

Postgraduate Researcher, Brunel University School of Health Science & Social Care,
E-mail: james.ashworth-beaumont@brunel.ac.uk
Tel: 0772 305 3199

Project Academic Supervisor:

Dr Alexander Nowicky,
Brunel University, School of Health Science & Social Care
E-mail: alexander.nowicky@brunel.ac.uk
Tel: 0189 526 8813

If you wish to speak to someone about this research project, but who is independent of the research team, contact:

Dr Iva Hauptmannova,

Research and Development Manager
R&D Office
Royal National Orthopaedic Hospital NHS Trust
UCL Institute of Orthopaedics and Musculoskeletal Science
Brockley Hill
Stanmore
HA7 4LP

E-mail: iva.hauptmannova@rnoh.nhs.uk; Tel: 020 8909 5529

Pilot study participant assessment checklist

Brunel UNIVERSITY WEST LONDON
School of Health Sciences and Social Care
Brunel University,
Uxbridge
Middlesex UB8 3PH
Telephone: +44 (0)1895 274000
Web www.brunel.ac.uk

Participant Name _____

Assessment date_____

Project Title

Effects of anodal tDCS on skill learning in relation to the non-dominant upper limb of incomplete cervical spinal cord injured subjects: a pilot study

Participant assessment proforma

Confirm criterion pass as suitable with **√** or fail with **X**

Inclusion criteria - checklist

- ☐ Age range 18-70, male or female *(declaration);*
- ☐ >12 months post-injury *(history);*
- ☐ Can converse in English and understand materials written in English language *(demonstrated);*
- ☐ Right-hand dominance prior to spinal cord injury *(declaration);*
- ☐ Ability to grasp small objects using the non-dominant (left) hand, including the use of tenodesis grip or an existing wrist orthosis if necessary *(demonstrated);*
- ☐ Stable medical condition *(based on history and questionnaire);*
- ☐ Incomplete SCI classification C/D, ASIA level of impairment C5-C7 *(assess);*

Exclusion criteria

- ☐ Cognitive impairment, *as detected by General Practitioner Cognitive (GPCOG) assessment tool;*
- ☐ Positive declaration for health issues - see *health questionnaire.*

☐ Passed suitable for study inclusion? (Y or N)

Edinburgh handedness inventory (modified)

------ **Analysis:** Investigator use only----------

Edinburgh Handedness Inventory (revised) *(Dragovic, 2004b)*					
Please mark the box that best describes which hand you use for the activity in question					
	Always left	Usually left	No preference	Usually right	Always right
Writing					
Throwing					
Scissors					
Toothbrush					
Knife (without fork)					
Spoon					
Match (striking)					
Computer mouse					

Response weighting: In accordance with the original version of the Edinburgh Handedness Inventory (Oldfield, 1971), do not score "no preference" responses and total right and left responses separately, counting "usually scores singly and "always" responses as double scores.

Left score	Right score

With two totals *R* and *L,* the Laterality Quotient (*LQ*) is defined :-

LQ = $\frac{R-L}{R+L}$*100 = — *100 =

LQ

This is not an exclusion criterion for the study.

Note:

In the event of the inability to write, drawing could still be used as a *substitute* for writing.

These two activities are very highly correlated (Dragovic, 2004).

ASIA sensory motor assessment sheet

MUSCLE GRADING

0 total paralysis

1 palpable or visible contraction

2 active movement, full range of motion, gravity eliminated

3 active movement, full range of motion, against gravity

4 active movement, full range of motion, against gravity and provides some resistance

5 active movement, full range of motion, against gravity and provides normal resistance

5* muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were not present

NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture.

ASIA IMPAIRMENT SCALE

☐ **A = Complete**: No motor or sensory function is preserved in the sacral segments S4-S5.

☐ **B = Incomplete:** Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.

☐ **C = Incomplete:** Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.

☐ **D = Incomplete:** Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

☐ **E = Normal:** Motor and sensory function are normal.

CLINICAL SYNDROMES (OPTIONAL)

☐ Central Cord
☐ Brown-Sequard
☐ Anterior Cord
☐ Conus Medullaris
☐ Cauda Equina

STEPS IN CLASSIFICATION

The following order is recommended in determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
2. Determine motor levels for right and left sides.
   Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level.
3. Determine the single neurological level.
   This is the lowest segment where motor and sensory function is normal on both sides, and is the most cephalad of the sensory and motor levels determined in steps 1 and 2.
4. Determine whether the injury is Complete or Incomplete (sacral sparing).
   If voluntary anal contraction = **No** *AND all S4-5 sensory scores* = **0** *AND any anal sensation* = **No**, *then injury is COMPLETE. Otherwise injury is incomplete.*
5. Determine ASIA Impairment Scale (AIS) Grade:
   Is injury Complete? If **YES**, AIS=A Record ZPP (For ZPP record lowest dermatome or myotome on each side with some (non-zero score) preservation)
   NO ↓
   Is injury motor incomplete? If **NO**, AIS=B (Yes=voluntary anal contraction OR motor function more than three levels below the motor level on a given side.)
   YES ↓
   Are at least half of the key muscles below the (single) neurological level graded 3 or better?
   NO ↓ AIS=C
   YES ↓ AIS=D

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

Patient Name _____

Examiner Name _____ Date/Time of Exam_____

STANDARD NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

ISCOS

MOTOR

KEY MUSCLES (scoring on reverse side)

	R	L	
C5			Elbow flexors
C6			Wrist extensors
C7			Elbow extensors
C8			Finger flexors (distal phalanx of middle finger)
T1			Finger abductors (little finger)

UPPER LIMB TOTAL (MAXIMUM) (25) (25) (50)

Comments:

L2			Hip flexors
L3			Knee extensors
L4			Ankle dorsiflexors
L5			Long toe extensors
S1			Ankle plantar flexors

Voluntary anal contraction (Yes/No)

LOWER LIMB TOTAL (MAXIMUM) (25) (25) (50)

SENSORY

KEY SENSORY POINTS

	LIGHT TOUCH R	LIGHT TOUCH L	PIN PRICK R	PIN PRICK L
C2				
C3				
C4				
C5				
C6				
C7				
C8				
T1				
T2				
T3				
T4				
T5				
T6				
T7				
T8				
T9				
T10				
T11				
T12				
L1				
L2				
L3				
L4				
L5				
S1				
S2				
S3				
S4-5				

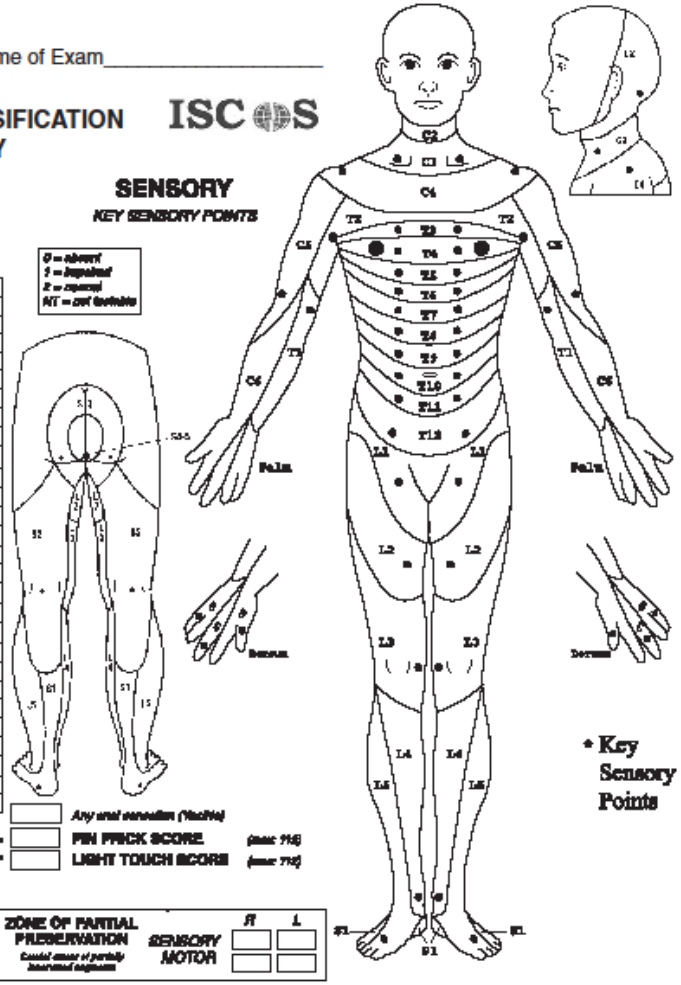
0 = absent
1 = impaired
2 = normal
NT = not testable

Any anal sensation (Yes/No)

TOTALS (MAXIMUM) (56) (56) (112) (112)

PIN PRICK SCORE (max: 112)

LIGHT TOUCH SCORE (max: 112)



* Key Sensory Points

NEUROLOGICAL LEVEL	SENSORY R	SENSORY L	COMPLETE OR INCOMPLETE?	ZONE OF PARTIAL PRESERVATION	SENSORY R	SENSORY L
The most caudal segment with normal function	MOTOR	MOTOR	Incomplete = Any sensory or motor function in S4-5	Caudal extent of partially innervated segments	MOTOR	MOTOR
			ASIA IMPAIRMENT SCALE			

This form may be copied freely but should not be altered without permission from the American Spinal Injury Association.

REV 02/04

Pilot study health questionnaire

Brunel
UNIVERSITY
WEST LONDON
School of Health Sciences and Social Care
Brunel University,
Uxbridge
Middlesex UB8 3PH
Telephone: +44 (0)1895 274000
Web www.brunel.ac.uk

Participant Primary Health Questionnaire

(for use at start of session 1)

Project Title

Effects of anodal tDCS on skill learning in relation to the non-dominant upper limb of incomplete cervical spinal cord injured subjects: a pilot study

Ethical approval

This study has received ethical approval from the Research Ethics Committee of Brunel University School of Health Sciences and Social Care and the NHS North London Research Ethics Committee 2.

Confidential Health Screening Questionnaire

Please provide your answers to the following questions, which relate toaspects of your health. We wish to ensure that you are fit and healthy to take part in this study. Indicate your responses by circling 'Yes' or 'No'.

If you answer 'yes' to any of the questions or are unsure of your answer, you should not continue to participate in this study.

(Questionnaire developed from Keel et al (2001))

Question		Response	
1	I feel unwell today	Yes	No
2	I have a respiratory condition other than asthma	Yes	No
3	I have a diagnosed skin condition (e.g. severe eczema)	Yes	No
4	I have a currently unstable medical condition and/or am symptomatic for	Yes	No

	autonomic dysreflexia		
5	I have an orthopaedic condition affecting the arms or hands	Yes	No
6	I have a heart condition and/or have a heart pacemaker	Yes	No
7	I have suffered a head injury requiring hospital admission	Yes	No
8	I have suffered a stroke or TIA*	Yes	No
9	I have undergone surgery to the skull (neurosurgery)	Yes	No
10	I have an aneurysm clip or other device in my head	Yes	No
11	I have previously suffered an epileptic fit or seizure	Yes	No
12	I have a diagnosed neurological condition affecting brain function	Yes	No
13	I suffer regular headaches (e.g. migraine)	Yes	No
14	I am pregnant	Yes	No
15	I have some other concern about my health	Yes	No

* Transient Ischaemic Attack – a short lasting, stroke-like event

If you have been able to answer 'No' to **all** of the above questions then you may continue to participate in this study.

Please be advised that brain stimulation techniques may have unpredictable effects if applied in conjunction with recreational drugs which affect brain function, including alcohol.

Please remember that your participation is entirely voluntary. If you have any concerns at any time please feel free to voice them immediately. You may withdraw your consent to continue at any time before or during any sessions. You do not have to provide a reason for doing so. If you are a patient, please be assured that your status as such will not be affected in any way, if you do choose to withdraw from this study.

Risks and Discomfort

This study will involve non-invasive stimulation of the brain with a low-intensity direct current (tDCS) technique. This brain stimulation technique has been shown to be safe and without long-term risk to study participants. Some short lasting side-effects have been reported by some participants. These side-effects include mild tingling, itching or burning sensations. Symptoms of mild headache, fatigue and difficulty in concentrating have also occasionally been reported.

Your safety and comfort is paramount. Before the testing sessions take place you will be asked to check and sign the consent form overleaf, ensuring that you still meet the health screening criteria for inclusion in this study. Additionally, in the event of any pain or discomfort during the session please report this and the session will be terminated immediately.

For further information, please do not hesitate to contact:

Chief Investigator

Jim Ashworth-Beaumont

Postgraduate Researcher,

Brunel University, School of Health Science & Social Care

E-mail: james.ashworth-beaumont@brunel.ac.uk

Tel: 0772 305 3199

Academic Supervisor

Dr Alexander Nowicky

Brunel University, School of Health Science & Social Care

E-mail: Alexander.nowicky@brunel.ac.uk

Tel: 0189 526 8753

Reference:

Brunel
UNIVERSITY
WEST LONDON
School of Health Sciences and Social Care
Brunel University,
Uxbridge
Middlesex UB8 3PH
Telephone: +44 (0)1895 274000
Web www.brunel.ac.uk

Consent Form

Project title: Effects of anodal tDCS on skill learning in relation to the non-dominant upper limb of incomplete cervical spinal cord injured subjects: a pilot study

Chief Investigator: Jim Ashworth-Beaumont

James.ashworth-beaumont@brunel.ac.uk

Tel: 07723 053199

Consent Form – Archive copy for Research Site file

Participant Statement

Please read this form carefully. Please voice any questions or concerns you may have. Remember that you are free to withdraw your consent at any time before or during each session. Please indicate your agreement to each statement by *initialling the corresponding box.*

1. I have read the Research Participant Information Sheet ☐

2. I consent to my GP and Consultant being informed about my inclusion in this study. ☐

3. I understand that my participation in this study is entirely voluntary. ☐

4. I understand that I am free to withdraw from participation in this study at any time without giving any reason, without my medical care or legal rights being affected. ☐

5. I understand that my identity will not be referred to or revealed in any published documentation arising from this study. ☐

6. I agree to the anonymised data arising from this study being stored beyond the completion date, for use in further research and educational studies. ☐

I understand the information contained in the Research Participant Information Sheet and this Consent Form. I give my consent to participate in this study.

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

Duplicate copies were provided to participant and inserted to medical notes

Subjectives Questionnaire

For administration directly after each training/stimulation session
Study title: The lasting effect of adjunctive tDCS on non-dominant skill learning and associated cortical excitability in healthy adults

Subjective Questionnaire

Subject no:
Day 1 2

Please answer the following questions in relation to the session you just completed

Indicate your selections by circling the appropriate response

Were you aware of any unusual TINGLING sensation during the session?

NO
YES

If YES, rate the intensity of **TINGLING** you felt:

very mild moderate very severe

1	2	3	4	5

and state the location:

……

Were you aware of any unusual ITCHING sensation during the session?

NO
YES

If YES, rate the intensity of **ITCHING** you felt:

very mild moderate very severe

1	2	3	4	5

and state the location:

……

Were you aware of any unusual BURNING sensation during the session?

NO
YES

If YES, rate the intensity of **BURNING** you felt:

very mild moderate very severe

1	2	3	4	5

and state the location:

……

Were you aware of any unusual PAIN sensation during the session?

NO
YES

If YES, rate the intensity of **PAIN** you felt:

very mild moderate very severe

1	2	3	4	5

and state the location:

……

Were you aware of any unusual HEADACHE during the session?

NO
YES

If YES, rate the intensity of **HEADACHE** you felt:

very mild moderate very severe

1	2	3	4	5

and state the location:

……

Were you aware of any unusual FATIGUE during the session?

NO
YES

If YES, rate the intensity of **FATIGUE** you felt:

very mild moderate very severe

1	2	3	4	5

and state the location:

……

Were you aware of any DIFFICULTY CONCENTRATING during the session?

NO
YES

If YES, rate the intensity of **DIFFICULTY CONCENTRATING** you felt by circling the appropriate number:

very mild moderate very severe

1	2	3	4	5

and state the location:

……

Were you aware of any unusual NERVOUSNESS during the session?

NO
YES

If YES, rate the intensity of **NERVOUSNESS** you felt by circling the appropriate number:

very mild moderate very severe

1	2	3	4	5

and state the location:

……

Were you aware of any unusual CHANGES IN VISUAL PERCEPTION during the session?

NO
YES

If YES, rate the intensity of **CHANGES IN VISUAL PERCEPTION** you felt by circling the appropriate number:

very mild moderate very severe

1	2	3	4	5

and state the location:

……

Were you aware of any UNPLEASANT SENSATION during the session?

NO
YES

If YES, rate the intensity of the **UNPLEASANT SENSATION** you felt:

very mild moderate very severe

1	2	3	4	5

and state the location:

…….

Were you aware of ANY OTHER PERCEPTIONS during the session?

NO
YES

If YES, rate the intensity of **ANY OTHER PERCEPTIONS** you felt:

very mild moderate very severe

1	2	3	4	5

Please describe what you felt and where:

…….

Finally, based on your experiences, can you guess whether you received active or sham/placebo tDCS stimulation today?

Please rate your judgement below:

Placebo stimulation unsure Active stimulation

1	2	3	4	5

Thank you for completing this questionnaire

Study 3

School of Health Sciences
and
Social Care
Brunel University,
Uxbridge
Middlesex UB8 3PH
Telephone: +44 (0)1895 274000

Participant Primary Health Questionnaire

(for use at start of session 1)

Study title

The lasting effect of adjunctive tDCS on non-dominant skill learning and associated cortical excitability in healthy adults

Ethical approval

This study has received ethical approval from the Research Ethics Committee of Brunel University School of Health Sciences and Social Care, Brunel University.

Confidential Health Screening Questionnaire

Please provide your answers to the following questions, which relate toaspects of your health. We wish to ensure that you are fit and healthy to take part in this study. Indicate your responses by circling 'Yes' or 'No'.

If you answer 'yes' to any of the questions or are unsure of your answer, please discuss this with the investigator conducting the session.

(Questionnaire developed from Keel et al (2001))

Question		Response	
1	I feel unwell today	Yes	No
2	I have a diagnosed skin condition (e.g. severe eczema)	Yes	No
3	I have an orthopaedic condition affecting my arm joints	Yes	No
4	I have a heart condition and/or have a heart pacemaker	Yes	No
5	I have suffered a head injury requiring hospital admission	Yes	No
6	I have suffered a stroke or TIA*	Yes	No

7	I have undergone surgery to the skull (neurosurgery)	Yes	No
8	I have an aneurysm clip or other device in my head	Yes	No
9	I have previously suffered an epileptic fit or seizure	Yes	No
10	I have a diagnosed neurological condition affecting brain function	Yes	No
11	I suffer regular headaches (e.g. migraine)	Yes	No
12	I am pregnant	Yes	No
13	I have some other concern about my health	Yes	No

* Transient Ischaemic Attack – a short lasting, stroke-like event

If you answer 'yes' to any of the questions or are unsure of your answer, please discuss this with the investigator conducting the session.

Please be advised that brain stimulation techniques may have unpredictable effects if applied in conjunction with recreational drugs which affect brain function, including alcohol.

Please remember that your participation is entirely voluntary. If you have any concerns at any time please feel free to voice them immediately. You may withdraw your consent to continue at any time before or during any sessions. You do not have to provide a reason for doing so. If you are a patient, please be assured that your status as such will not be affected in any way, if you do choose to withdraw from this study.

Risks and potential for discomfort

This study involves non-invasive stimulation of the brain with a low-intensity direct current (tDCS) technique. This brain stimulation technique has been shown to be safe and without long-term risk to study participants. Some short lasting side-effects have been reported by some participants. These side-effects include mild tingling, itching or burning sensations. Symptoms of mild headache, fatigue and difficulty in concentrating have also been reported on rare occasions.

We are also using transcranial magnetic stimulation (TMS) as a means of measuring the strength of connections between the brain and arm muscles. All the published evidence shows that the technique to be used in this study causes no adverse effects, and is safe and painless to apply in healthy adults who meet the health criteria laid out in the questionnaire you have just completed.

Your safety and comfort is paramount. Before this study begins we ask you to check and sign the consent form which follows. Always remember that, in *the event of any pain or discomfort during your participation in this study, you should report this to the investigator conducting the session. The session will be halted immediately.*

Reference:

Primary Consent Forms

Study title: The lasting effect of adjunctive tDCS on non-dominant skill learning and associated cortical excitability in healthy adults

Chief Investigator: Jim Ashworth-Beaumont

James.ashworth-beaumont@brunel.ac.uk

Tel: 07723 053199

Brunel UNIVERSITY WEST LONDON
School of Health Sciences and Social Care
Brunel University,
Uxbridge
Middlesex UB8 3PH
Telephone: +44 (0)1895 274000
Web www.brunel.ac.uk

Consent Form – Archive copy for Research Site file

Participant Statement

Please read this form carefully. Please voice any questions or concerns you may have. Remember that you are free to withdraw your consent at any time before or during each session. Please indicate your agreement to each statement by *initialling the corresponding box.*

1. I have read the Research Participant Information Sheet ☐

2. I consent to my GP and Consultant being informed about my inclusion in this study. ☐

3. I understand that my participation in this study is entirely voluntary. ☐

4. I understand that I am free to withdraw from participation in this study at any time without giving any reason, without my medical care or legal rights being affected. ☐

5. I understand that my identity will not be referred to or revealed in any published documentation arising from this study. ☐

6. I agree to the anonymised data arising from this study being stored beyond the completion date, for use in further research and educational studies. ☐

7. I understand that the reward of £35 is payable only after completion of the full 3 day study protocol. ☐

I understand the information contained in the Research Participant Information Sheet and this Consent Form. I give my consent to participate in this study.

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

This Consent Form copy is to be retained at the study site

A duplicate copy was provided to the participant.

Appendix F. Study 3Experimental protocol

Day	**Activity**	**Time (minutes)**	
1	Screening and consent	20	
Participant preparation		10	
Determination of MVC, resting and active motor thresholds, recruitment and facilitation curves		35	
JTHFT behavioural measure administration x 2		10	
Anodal tDCS preparation		10	
MSRT training/tDCS administration		45	
Subjective questionnaire		10	
Day total		***140***	
2	Screening and consent	10	
Anodal tDCS preparation		10	
MSRT training/tDCS administration		45	
Determination of MVC, resting and active motor thresholds, recruitment and facilitation curves		35	
Subjective questionnaire		10	
Day total		***110***	
3	Screening and consent	10	
Participant preparation		10	
Determination of MVC, resting and active motor thresholds, recruitment and facilitation curves		35	
JTHFT behavioural measure administration x 2		10	
MSRT administration 4 x 10 trials		15	
Day total		***80***	
Grand total		**320 = 5 hours 30 minutes**	

Appendix G. Study 3 TMS measurement protocol subroutines

Preparation:

Clean skin – apply electrodes to APB and mDelt

EMG at MVC – calibrate lightbox
EMG at MVC – run config file MVC RECORDING ONLY 1 SEC CYCLE.SGC and record minimum 6 frames. Save separately for each muscle

Measure vertex
TMS 90mm single round coil PN 9784-00 – apply to vertex

Determine RMT and AMT for APB
Determine RMT and AMT for mDelt
During 1st session:
Enter values to INTENSITY RECORD EXCEL template and print off

Measures:

Recruitment curve – resting APB

Load NEW HEALTHY TDCS RECRUITMENT CURVE APB.SGC
At baseline, enter stim intensity values from INTENSITY RECORD EXCEL template. Autosave setting to subject file. DDMMYYxx00.
Save configuration file to subject folder for reuse at repeat measure intervals.
Apply coil and run program.
Finish file/enter comment.

Facilitated curve – active APB 20% MVC EMG

Load NEW HEALTHY TDCS APB FACILITATED recruitment curve.SGC
At baseline, enter stim intensity values from INTENSITY RECORD EXCEL template. Autosave setting to subject file. DDMMYYxx00.
Save configuration file to subject folder for reuse at repeat measure intervals.
Apply coil and run program.
Finish file/enter comment.

Facilitated curve – active mDelt 20% MVC EMG

Load NEW HEALTHY TDCS mDelt FACILITATED recruitment curves.SGC
At baseline, enter stim intensity values from INTENSITY RECORD EXCEL template. Autosave setting to subject file. DDMMYYxx00.
Save configuration file to subject folder for reuse at repeat measure intervals.
Apply coil and run program.
Finish file/enter comment.

FOR FOLLOW-UP MEASURES, LOAD THE CONFIG FILES WITHIN SUBJECT FILES SAVED FROM BASELINE MEASURES

“Success is never final, failure is never fatal. It's courage that counts.”

- John Wooden