UNIVERSITY OF SOUTHAMPTON

FACULTY OF HEALTH SCIENCES

THE EFFECT OF COMBINING TRANSCRANIAL DIRECT CURRENT STIMULATION WITH ROBOT THERAPY FOR THE IMPAIRED UPPER LIMB IN STROKE

by

Lisa Tedesco Triccas

Thesis for the degree of Doctor of Philosophy

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ABSTRACT

FACULTY OF HEALTH SCIENCES

Doctoral of Philosophy

THE EFFECT OF COMBINING TRANSCRANIAL DIRECT CURRENT STIMULATION WITH ROBOT THERAPY FOR THE IMPAIRED UPPER LIMB IN STROKE

Lisa Tedesco Triccas

Neurological rehabilitation technologies such as Robot Therapy (RT) and non-invasive brain stimulation (NIBS) can promote motor recovery after stroke. The novelty of this research was to explore the feasibility and the effect of the combination method of NIBS called transcranial Direct Current Stimulation (tDCS) with uni-lateral and three-dimensional RT for the impaired upper limb (UL) in people with sub-acute and chronic stroke.

This thesis involved three studies: (a) systematic review with meta-analyses (b) a pilot double-blinded randomised controlled trial with a feasibility component and (c) a reliability study of the measurement of Motor Evoked Potential (MEP) response using Transcranial Magnetic Stimulation in healthy adults. The first study involved a review of seven papers exploring the combination of tDCS with rehabilitation programmes for the UL in stroke. For the second study, stroke participants underwent 18 x one hour sessions of RT (Armeo®) over eight weeks during which they received 20 minutes real tDCS or sham tDCS. Outcome measures were applied at baseline, post-intervention and at three-month follow-up. The qualitative component explored the views and experiences of the participants of RT and NIBS using semi-structured interviews. The third study involved age-matched healthy adults exploring intra-rater and test-retest reliability of the TMS assessment.

Results of the three studies were the following: Seven papers were reviewed and a small effect size was found favouring real tDCS and rehabilitation programmes for the UL in stroke. 22 participants (12 sub-acute and 10 chronic) completed the pilot RCT. Participants adhered well to the treatment. One participant dropped out of the trial due to painful sensations and skin problems. The sub-acute and chronic groups showed a clinically significant improvement of 15.5% and 8.8% respectively in UL impairments at post-intervention from baseline. There was no difference in the effects of sham and anodal tDCS on UL impairments. Participants found the treatment beneficial and gave suggestions how to improve future research. In summary, the TMS assessment showed excellent reliability for measurement of resting motor threshold but poor to moderate reliability for MEP amplitude.

In conclusion, it was indicated that RT may be of benefit in sub-acute and chronic stroke however, adding tDCS may not result in an additive effect on UL impairments and dexterity. The present study provided a power calculation for a larger RCT to be carried out in the future.

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Academic thesis: Declaration of authorship

I, Lisa Tedesco Triccas, declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

[The effect of combining transcranial direct current stimulation and robot therapy for the impaired upper limb in stroke]

I confirm that:

1. This work was done wholly while in candidature for a research degree at this University;

2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;

3. Where I have consulted the published work of others, this is always clearly attributed;

4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;

5. I have acknowledged all main sources of help;

6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;

7. Parts of this work have been published as:

Tedesco-Triccas L, Burridge J, Hughes AM, Verheyden G, Rothwell J (2011) Combining transcranial Direct Current Stimulation with robot therapy for the impaired upper limb after sub-acute stroke Clinical Neurophysiology Volume 122: Supplement 1 pg: S149

Signed:

Date:

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Investing in your future

List of abbreviations

AD= Anterior Deltoid

ADLs= Activities of Daily Living

ARAT= Action Research Arm Test

ANOVA= Analysis of Variance

BBT= Box and Block Test

BDNF= Brain-Derived Neurotrophic Factor

CG=Chronc Group

CI= Confidence Interval

CIMT= Constraint Induced Movement Therapy

ED= Extensor Digitorum

EMG= Electromyography

FMA= Fugl-Meyer Assessment

fMRI= functional Magnetic Resonance Imaging

GABA= *gamma*-Aminobutyric acid

HAD= Hospital Anxiety and Depression Scale

HPR= Hand Path Ratio

Hz= Hertz

ICC=Intraclass Coefficient

JTT= Jebsen-Taylor Hand Function Test

mA= milliAmperes

mV= millivolts

LTD=Long-Term Depressopm

LTP= Long-Term Potentiation

MAL= Motor Activity Log-28

MAS= Modified Ashworth Scale

MBI= Modified Barthel Index

MDC= Minimal Detectable Change

MEP= Motor Evoked Potential

μV= microVolt

MTS= Modified Tardieu Scale

NIBS= Non-Invasive Brain Stimulation

NHS= National Health Service

NMDA=*N*-methyl-D-aspartic acid

OA= Older Adults

RCT= Randomised Controlled Trial

REC= Research Ethics Committee

RevMan= Review Manager Program

rTMS= repetitive Transcranial Magnetic Stimulation

RT= Robot Therapy

tDCS= transcranial Direct Current Stimulation

SD= Standard Deviation

SEM= Standard Error of Mean

SG= Sub-acute Group

SIS= Stroke Impact Scale 3.0

TMS= Transcranial Magnetic Stimulation

UK= United Kingdom

UL= Upper Limb

WHO= World Health Organisation

WMFT= Wolf Motor Function Test

YA= Young Adults

Abbreviations of researchers:

AMH= Dr Ann-Marie Hughes

GV= Dr Geert Verheyden

JHB= Professor Jane Helena Burridge

KM= Dr Katie Meadmore

LTT= Miss Lisa Tedesco Triccas

MDH= Dr Maggie Donovan-Hall

Chapter 1

Introduction

1.1 Overview

This chapter gives an overview of the thesis by presenting a summary of the background and the research that was carried out as part of this Doctorate of Philosophy degree.

1.1.1 Background

Strokeis a worldwide public health concern and one of the main causes of disability (Kolominsky-Rabas et al., 2001, Albert and Kesselring, 2012). According to the World Health Organisation (WHO), in Europe, due to demographic changes, by 2025 the number of stroke events is likely to be more than 1.5 million per year (Truelsen et al., 2006). Within the United Kingdom (UK), the crude incidence of first-time stroke affects around 160 people per 100,000 of the population (Rothwell et al., 2005). However, in the UK, stroke incidence decreased by 30% between 1998 to 2008 (Lee et al., 2011). This is due to reduction of risk factors such as diabetes and high cholesterol, hypertension, obesity and management of atrial fibrillation (Goldstein et al., 2011). In addition, improved treatment and rehabilitation has led to an increase in stroke survival (Zhang et al., 2012).

With the high numbers of people experiencing a stroke, disability is a major global health problem (Clarke, 1999, Boggio et al., 2007). At six months post-stroke, 33% to 66% do not present with recovery of Upper Limb (UL) function (Kwakkel et al., 2003, Kwakkel and Kollen, 2013). At 5 years post- stroke, 25% of the people report that they have difficulty using the affected limb during activities (Geddes et al., 1996).

1.1.2 Rationale for the proposed research

A large amount of rehabilitation time is spent on improving function and independence of stroke survivors (Lu et al., 2011b). In order to increase function and reduce impairment, UL rehabilitation focuses on encouraging movement of the arm and hand using various approaches. With 6% of the National Health Service (NHS) budget allocated to stroke care, it is therefore important that the chosen rehabilitation approach is cost-effective (Rothwell, 2001).

Rehabilitation techniques used by specialists were devised to try and improve functional arm and hand use after stroke. There is no evidence showing which modality is superior over the other for the UL (Kollen et al., 2009, Loureiro et al., 2011). However, there is evidence showing that intensity leads to better UL recovery (Norouzi-Gheidari et al., 2012). In fact, rehabilitation regimes involving the UL after stroke such as constraint induced movement therapy or Robot Therapy (RT) focus on encouraging the use of the affected limb intensively during activities which can lead to an increased recovery of the UL function (Hallett, 2001, Summers et al., 2007). These modalities require a one-to-one therapist-patient relationship which can be costly but there has been evidence that RT can lead to lower overall healthcare use costs than traditional rehabilitation (Wagner et al., 2011).

Recent research in both animal and human models has demonstrated the potential of the damaged motor system to recover through changes in the neural system at synaptic level, leading to reorganisation, which is termed neuroplasticity (Dancause and Nudo, 2011). Intensity and repetitive movements could enhance neuroplasticity, however, resulting maladaptive changes such compensatory movement and ipsilateral motor inhibitory projections could result in poor recovery of the UL (Takeuchi and Izumi, 2012).

Functional improvement in people with of stroke has been shown to be associated with increased cortical excitability (Liepert et al., 2004). Non-Invasive Brain Stimulation (NIBS) such as transcranial direct current stimulation (tDCS) can promote cortical excitability and reorganisation. After application of tDCS, changes in the motor cortex have been associated with neuroplasticity due to changes at the N-methyl-D-aspartate (NMDA) receptors of the postsynaptic membranes (Nitsche et al., 2003a, Nitsche et al., 2006). This overall effect could thus facilitate motor learning and recovery (Malcolm et al., 2007, Stagg et al., 2011). Subsequently, since motor learning is more prone to occur in the first three to six months after the stroke it is optimal to integrate technologies such as RT and NIBS in the acute and sub-acute rehabilitation settings for people of stroke (Albert and Kesselring, 2012). On the other hand, recovery can even occur after six months post-stroke (Lo et al., 2010) and therefore, the effect of such technologies at different stages of a stroke, need to be addressed.

Recently, researchers have speculated whether the combination of NIBS with task-orientated therapy such as RT will result in an additive neuroplastic cortical effect and possibly an enhanced functional recovery after a neurological condition (Hesse et al., 2007, Edwards et al., 2009).

1.2 Main aim and objectives

The main aim of the research presented in this thesis was therefore to explore the effects of tDCS in addition with RT for the impaired UL involving people with sub-acute and chronic stroke.

The main objectives were:

- To explore the effect of multiple sessions of real tDCS versus sham tDCS in addition with rehabilitation on UL impairments and activities in people with stroke
- To explore the feasibility of applying anodal tDCS with unilateral and unpowered robot therapy (RT) in people with sub-acute and chronic stroke
- To compare the effect of anodal tDCS and RT with sham tDCS and RT on UL impairments, function, activities and participation after sub-acute and chronic stroke
- To compare the effect of anodal tDCS and RT with sham tDCS and RT on cortical excitability after sub-acute and chronic stroke
- To explore the views and experiences of non-invasive brain stimulation and RT by people with sub-acute and chronic stroke
- To test the intra-rater and test-retest reliability of cortical excitability (Resting Motor Threshold and Motor Evoked Potential amplitude) outcome measure of the deltoid and extensor digitorum muscles in healthy adults

1.3 Research undertaken

First, a systematic review with meta-analyses was carried out exploring the effects of tDCS on UL impairments in stroke. This latter research process formed the research question and rationale for the main research study. The type of research chosen for the main study was a mixed methods approach. The quantitative component was conducted through a pilot double-blinded randomised controlled trial, with a feasibility component. This latter trial involved three-dimensional and uni-directional Armeo®spring robot therapy in combination with tDCS for the impaired UL. The trial consisted of a two group design of participants with sub-acute and chronic stroke randomised to either go through Armeo® RT with real anodal tDCS, or Armeo® RT with sham tDCS. Each participant received an intervention programme of 18 sessions over an 8 week period. Each session consisted of twenty minutes of real or sham tDCS during one hour of RT. Clinical and neurophysiological measures using TMS were taken at baseline, post- intervention, and a three month follow-up. For the qualitative component, participants also took part in semi-structured interviews, which explored their views and experiences of NIBS and RT. Interviews were conducted after the post-intervention assessment.

In order to make accurate conclusions of the neurophysiological measurements involved in the RCT, it was concluded that a intra-rater and test-retest reliability of the MEP response involving healthy adults was needed to be carried out. Thus,the third section of the research involved a reliability study which was carried out as a final study to be included for the Doctorate of Philisophy degree.

1.4 Structure of the thesis

Overview of the presentation of this doctoral thesis is demonstrated in Figure 1.1. Chapter one introduced the research and topic and rationale for the study. Chapter two is a review of the literature that underpins the research and includes the following sections: stroke, neuroplasticity and motor learning, skill acquisition, rehabilitation and learning new skills in stroke and rehabilitation of upper limb impairments after stroke.

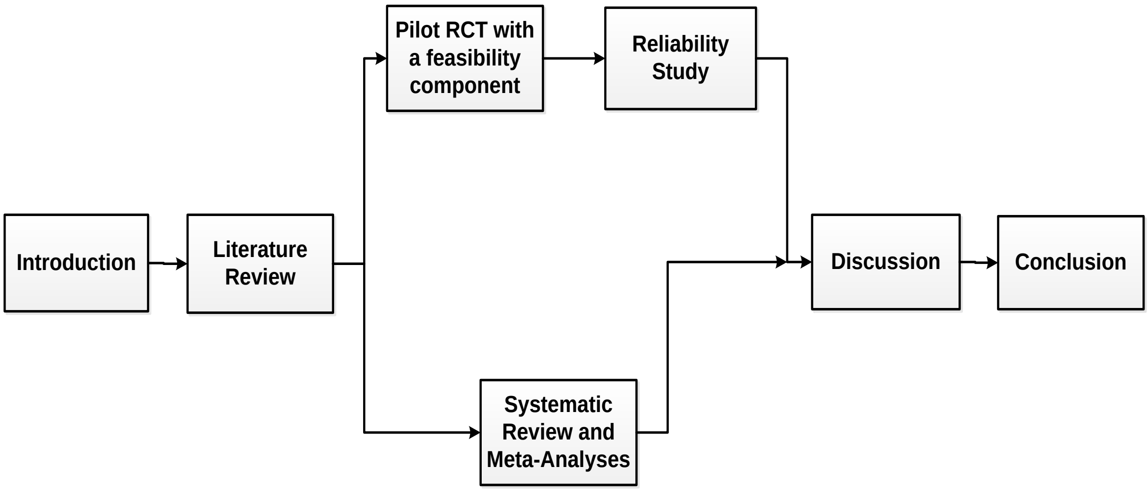

Figure 1.1 Overview of thesis

This is followed by specific topics concerning the evidence for RT and the effect of NIBS for the impaired UL after stroke. Based on an understanding of current neurophysiology and evidence from the literature, the research question is presented followed by description and justification of the outcome measures used. Chapter three includes a systematic review and meta-analyses. Chapter four presents the research methodology and the results of the pilot RCT (involving a quantitative and qualitative component). This is be followed by Chapter five presenting a reliability study of the measurement of cortical excitability involving 21 healthy adults including the background, methodology, and the results from this study. Chapter six discusses the feasibility issues, findings and limitations from the whole research process. Chapter seven presents the implications for clinical practice and future work. Chapter eight presents the general conclusion followed by the appendices, references and glossary.

1.5 Publications and presentations

This section presents a list of the journal publications and oral and poster presentations from attended conferences, summer schools and future conferences.

1.5.1 Abstract publication

Tedesco-Triccas L, Burridge J, Hughes AM, Verheyden G, Rothwell J (2011) Combining transcranial Direct Current Stimulation with robot therapy for the impaired upper limb after sub-acute stroke Clinical Neurophysiology Volume 122: Supplement 1 pg: S149

1.5.2 Oral presentations

Tedesco Triccas L, Burridge J, Hughes AM, Desikan M, Verheyden G, Rothwell J (2013) Combining Non-Invasive Brain Stimulation with Unilateral and Three-dimensional Robot Therapy for the Impaired Upper Limb in Sub-Acute stroke *Post-graduate Faculty of Health Sciences Conference, University of Southampton, June 2013, Southampton UK*

Tedesco Triccas L, Burridge J, Hughes AM, Desikan M, Verheyden G, Rothwell J (2014) Combining non-invasive brain stimulation with unilateral and three-dimensional robot therapy for the impaired upper limb in stroke rehabilitation *European Stroke Conference, May 2014, Nice, France*

1.5.3 Poster presentations

a) Tedesco-Triccas L, Burridge J, Hughes AM, Verheyden G, Rothwell J (2011) Combining transcranial Direct Current Stimulation with robot therapy for the impaired upper limb after sub-acute stroke. *Southampton Neurosciences Group Annual Conference, Life Sciences, University of Southampton, September 2011, Southampton, UK*

b) Tedesco-Triccas L, Burridge J, Hughes AM, Verheyden G, Rothwell J (2012) Combining transcranial Direct Current Stimulation with robot therapy for the impaired upper limb after sub-acute stroke. *Research in Primary and Community Healthcare Settings: Showcasing the Patient Benefit Conference organised by Southampton and Solent NHS trust, April 2012, Southampton, UK*

c) Tedesco-Triccas L, Burridge J, Hughes AM, Verheyden G, Rothwell J (2012) Combining Non-Invasive Brain Stimulation with unilateral and three-dimensional robot therapy for the impaired upper limb in early stroke rehabilitation *TMS Summer School, May 2012, Oxford, UK.*

d) Tedesco Triccas L, Burridge J, Hughes AM, Desikan M, Verheyden G, Rothwell J (2013) Combining Non-Invasive Brain Stimulation with Unilateral and Three-dimensional Robot Therapy for the Impaired Upper Limb in Sub-Acute stroke *Society For Research in Rehabilitation Meeting, February 2012, Bath, UK*

e) Tedesco-Triccas L, Burridge J, Hughes AM, Verheyden G, Desikan M, Rothwell J (2013) Combining Non-Invasive Brain Stimulation with unilateral and three-dimensional robot therapy for the impaired upper limb in early stroke rehabilitation (preliminary results) *TMS Summer School, May 2013, Oxford, UK*

f) Tedesco Triccas L, Burridge J, Hughes AM, Verheyden G, Desikan M, Rothwell J (2014) A randomised controlled trial combining transcranial direct current stimulation with unilateral and three dimensional robot therapy for the impaired upper limb in stroke *World 8th World Congress for NeuroRehabilitation, April 2014, Istanbul, Turkey*

g) Tedesco Triccas L, Burridge J, Hughes AM, Pickering R, Verheyden G, Desikan M, Rothwell J (2014) A systematic review of the application of transcranial direct current stimulation and rehabilitation for the upper limb in stroke *World 8th World Congress for NeuroRehabilitation, April 2014, Istanbul, Turkey*

1.6 Conclusion

This chapter introduced the topic about UL impairments and limitations in activities of daily living experienced by people with stroke. It also presented some evidence about the application of RT and tDCS in stroke. The aims and objectives of the research were also presented followed by a brief explanation about the research that was carried out. The next chapter will focus on a detailed literature review followed by the formation of the research question and design for research presented in this thesis.

Chapter 2

Literature Review

2.1 Introduction

This chapter presents a detailed literature review focusing on topics such as stroke, neuroplasticity, learning and recovery, recovery and rehabilitation of UL impairments after stroke, Robot Therapy (RT) and Non-Invasive Brain Stimulation (NIBS). This is followed by formation of the research question and rationale for the research.

2.2 Stroke and risk factors

Stroke can be defined as:

"rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin" (Aho et al., 1980: 114).

Stroke is the third largest cause of death in the UK (after coronary heart disease and all cancers combined) and is responsible for 11% of deaths in England and Wales (NHS Gloucestershire Stroke Unit Report 2012) . International Stroke Incidence Collaboration found that in eight populations from Europe, Australia and the United States (3.5 million person-years, 5575 strokes), most strokes were of ischaemic origin (Sudlow et al., 1997).

This definition refers to signs and symptoms of the two types of stroke: ischaemic and haemorrhagic (sub-arachnoid or intracerebral). An ischaemic stroke is defined as: "An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction" (Sacco et al., 2013: 2066). A stroke caused by intracerebral haemorrhage is defined as:

"Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma" (Sacco et al., 2013: 2066).

On the other hand, a sub-arachnoid haemorrhagic is defined similarly to the intracerebral haemorrhage however bleeding occurs in the subarachnoid space and is associated with a headache. Out of 3000 people with stroke 78% were of ischaemic origin and 22% were of haemorrhagic origin (Lauretani et al., 2010, O'Donnell et al., 2010). Out of 2337 individuals with ischaemic stroke, 52% had a partial anterior circulation infarct, 29.5% had lacunar anterior circulation infarct, 21% had a posterior circulation infarct and 8% had a total anterior circulation infarct and (O'Donnell et al., 2010).

The most common recognised mechanisms for ischaemic stroke are: occlusion of small cerebral arteries in persons with hypertension, artery to artery embolism from the extracranial and intracranial arteries, an embolus to the brain of cardiac or aortic origin, and rarely, perfusion failure due to severe extracranial arterial stenosis and occlusion (Gorelick, 2002).

Major risk factors for ischaemic stroke can be modifiable or non-modifiable. Non-modifiable factors are age, male gender, race and inherited predisposition. Modifiable factors are hypertension, cardiac diseases, cigarette smoking, diabetes mellitus, cigarette smoking and cholesterol (Allen and Bayraktutan, 2008). Ischaemic strokes occur in 10% of the population at 45 years or younger and from 4467 young people with stroke, the major risks identified were smoking (55.5%), physical inactivity (48.2%) and atrial hypertension (46.6%). High-risk alcohol consumption (33.0%) and short sleep duration (20.6%) were more common in men, and migraine (26.5%) was more frequent in women (Nedeltchev et al., 2005, von Sarnowski et al., 2013). Major risk factors for haemorrhagic stroke (intracerebral haemorrhage) are race, male gender, advanced age, heavy use of alcohol, cocaine use, thrombolytic therapy and risk factor for subarachnoid haemorrhage are congenital defects, cigarette smoking and high blood pressure (Xi et al., 2006).

2.2.1 Stroke incidence, prevalence and cost of care

In England, there are approximately 110,000 newly diagnosed strokes and 30,000 recurrent strokes each year (NHS Gloucestershire stroke unit report, 2012). The risk of death from a first time stroke is about 12% at 7 days, 19% at one month and 30% at one year post-stroke. High and increasing stroke mortality is occurring in Eastern countries however, low and decreasing mortality is occurring in Western countries in Europe (Sarti et al., 2000).

Between 1981 and 2004, a decrease in stroke incidence in certain countries with high income, such as the United Kingdom (UK) was reported (Rothwell et al., 2004). This is due to an increased awareness of, and improved management of such risk factors of ischaemic and haemorrhagic stroke such as Type II diabetes, obesity and prescription of drugs controlling cardiovascular risk factors (Lee et al., 2011, Zhang et al., 2012). From the 1970s to 2000, in countries with middle to low income, however, the stroke incidence is 20% higher (Feigin et al., 2009).This is mainly due to the lack of promotion in preventative strategies and public health awareness in middle to low income countries such as Africa (Thrift and Arabshahi, 2012).

Acute care such as thrombolysis, decreases the mortality rate and disability after stroke, however, increases the total cost of care (Sundberg et al., 2003, Hacke et al., 2008). In the UK, it has been estimated that the total cost for stroke care is around nine billion pounds per year (Saka et al., 2009). This total cost includes approximately 49% annual direct care cost consisting of in-patient hospital stay, medication and also out-patient care such as nursing homes; 29% on informal care which includes carer costs and the indirect costs for pre-mature death which for people with stroke under 65 is approximately 24% (Saka et al., 2009). However, around half of the stroke survivors are left dependent on others whilst carrying out everyday activities. Most stroke survivors experience some form of disability that requires months of rehabilitation provided by the National Health Service (NHS). Each primary care trust spends £1.7 million per annum related to community care and rehabilitation of stroke (NHS Improvement Stroke, 2009). Therefore, the rationale of the research of this thesis targets problems of increasing health care costs and problems with disability after stroke.

2.2.2 Stroke and disability

Stroke results in long-term disability and, thus, being one of the primary reasons for psychosocial impact experienced by people with stroke, their families and the healthcare system (Aprile et al., 2008). The International Classification of Functioning, Disability and Health (ICF) model displays a framework for assessing the consequences of a health condition such as stroke in terms of function and disability (Figure 2.1) (WHO, 2001). This framework focusses on the pathology, impairment, activity (limitations) and participation (restrictions). This can have an impact on the life of the individual.

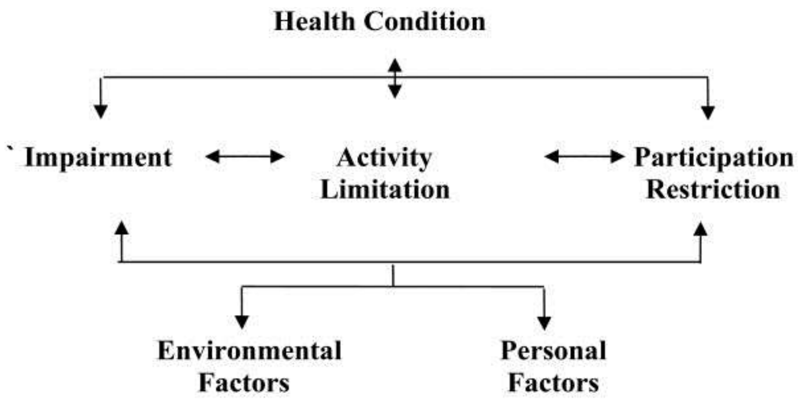

Figure 2.1 Conceptual framework of disability by the International Classification for Functioning, Disability and Health

(Scott et al., 2012)

Researchers suggested that the social theory and psychology of change following an acquired disability could be represented by a ‘Life Thread Model’ (Ellis-Hill et al., 2008). This model demonstrates that before a stroke, life can be portrayed as a complete life thread (first image of Figure 2.2). Daily life involves interaction with several people leading to parallel life threads intertwining (second image of Figure 2.2). However, after a condition such as a stroke the life thread becomes unravelled and individuals face psychosocial challenges (third image of Figure 2.2). Regardless of the severity, stroke impairments can restrict any forms of participation such as returning to work (Daniel et al., 2009).

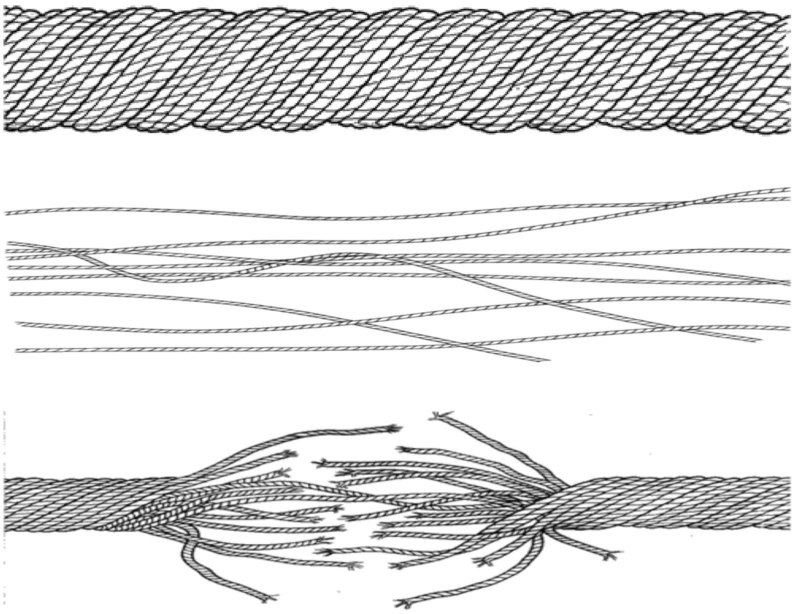

Figure 2.2 Life Thread Model demonstrating the experiences of a stroke

(Ellis Hill et al. 2008)

The main goal of people with stroke is to overcome these challenges and re-integrate in the community and back to work life. However, problems with emotion, language, memory and movement hinder stroke survivors to achieve this goal (Scott et al., 2012). Cognitive impairment, emotional problems and disability are the main causes of lack of participation in rehabilitation (Skidmore et al., 2010). People with stroke have problems carrying out Activities of Daily Living (ADLs) and thus require any form of assistance in the community (Hartman-Maeir et al., 2007). Assistance can potentially lead to social connection and inclusion which can thus increase the level of participation (Hammel et al., 2008). However, a recent study showed that out of 116 people at six months post-stroke, 12% still felt limitations in participation (Eriksson et al., 2013). Not only do people with stroke have to face psychosocial challenges but also physical problems such as motor deficits in the UL which is a major cause of disability after stroke (Yozbatiran et al., 2009).

2.2.3 Stroke and upper limb disability

Severe UL impairments are experienced by people with stroke due to a ischaemia or haemorrhage of the middle cerebral artery which is the main artery responsible for blood flow to the primary motor areas of the brain (Lu et al., 2011b). In the first month after a stroke, arm paresis is one of predictors of outcome of body functions and activities (Krakauer, 2005, Langhorne et al., 2011).

Only one third of stroke survivors regain a functional arm (Broeks et al., 1999). At four years post-stroke, 50% had a non-functional arm due to problems with dexterity (Dijkerman et al., 1996, Broeks et al., 1999). Recent studies reported that at six months post-stroke, 33% to 66% do not present with recovery of UL function and only a small percentage, 5-20% achieve full recovery (Kwakkel et al., 2003, Kwakkel and Kollen, 2013). People with stroke presenting with movement in the UL within four weeks post-stroke had 94% prediction of gaining dexterity. If the patient did not show any UL movement, people with stroke had only 10% prediction of gaining dexterity (Kwakkel and Kollen, 2013).

To gain UL and hand function: “proximal stability, prehensile strength, rapid finger movement and precise control of grip force and release” is required (Harvey and Stinear, 2010: S269). Thus, the movements required for UL function are complex (Kwakkel et al., 1999). Tonal changes at the UL such as flaccidity and spasticity also can result in loss of dexterity (Kwakkel et al., 2003, Dobkin, 2005). Due to such difficulties, people with stroke in the chronic stage rely on their unaffected arm to carry out daily activities and therefore, develop learned non-use in the affected arm and hand and also maladaptive neuroplasticity (Taub et al., 1994, Wolf et al., 2006).

2.3 Neuroplasticity and motor learning

This section focuses on the basic science underpinning neuroplasticity and its importance in motor recovery and stroke rehabilitation. In addition, factors needed for motor learning and recovery that can be integrated in rehabilitation are also discussed.

2.3.1 Neuroplasticity

The nervous system has the ability to change and adapt. It has various functions such as storing memories, receiving sensory stimuli and coordinating motor plans and these systems change and adapt depending on stimuli from the outside environment. Neuroplasticity is the term for the ability of the brain and the central nervous system to obtain new information and adjust to environmental change by changing its neural connectivity and function (Knaepen et al., 2010).

At the beginning of the 20th century, Santiago Ramón y Cajal stated that the nervous system is fixed and cells cannot be regenerated. After the mid- 20th century, the latter theory was disproved showing that the nervous system can change and adapt, formulating the term ‘neuroplasticity’ (y Cajal, 1928). In 1949, Donald O Hebb speculated that learning involves an association between a neural mechanism with enhanced synaptic connectivity (Hebb, 2002, Cooper 2005). Hebb also theorised that when both presynaptic and postsynaptic neurons fire together at the same time and repeatedly, their synaptic connections would be strengthened. Obeying the Hebbian rule, changes in synapse were demonstrated in sea slugs *Aplysia californica* after acquiring a memory (Frazier et al., 1967). This led to the discovery of Long-Term Potentiation (LTP) by Bliss and Lømo (1973) which proved Hebbian principles at a molecular level. Bliss and Lomo discussed that an enhanced synaptic efficacy and postsynaptic activity occurs when involving a single high-frequency tetanic burst of direct repetitive stimulation to the prefrontal fibre pathway in the anaesthetised rabbit hippocampus. Neuroplasticity mainly occurs by creation of new anatomical connections or by changes in synaptic morphology and efficacy (Møller, 2006).

2.3.2 Synaptic plasticity and Long term potentiation

Long Term Potentiation (LTP) is based on the long-lasting increase in synaptic efficacy after tetanic stimulation of the presynaptic neuron (Collingridge and Bliss, 1995). The long-lasting change is a result of presynaptic neurotransmitter release and increased postsynaptic receptor expression, the *N*-methyl-D-aspartic acid (NMDA) glutamate receptor.

The NMDA receptor is a ligand-gated calcium channel. The receptor is a binding site on the extracellular surface for glutamate (a neurotransmitter) that directs the opening of the channel. The channel is usually blocked by a Magnesium ion that can only be displaced when depolarisation of the post-synaptic neuron occurs.

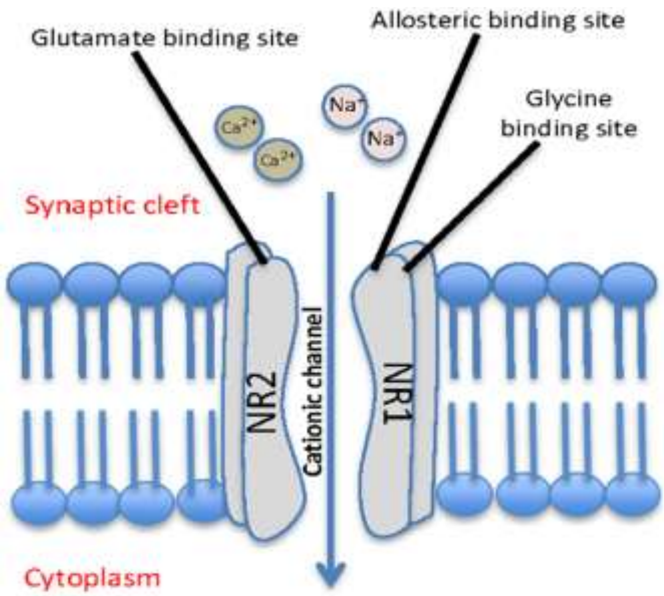

Figure 2.3 *N*-methyl-D-aspartic acid glutamate receptor

(Lakhan et al., 2013)

For the channel to be fully open, an influx of sodium (Na^+) and calcium (Ca^{2+}) ions enter the cell (Figure 2.3) (Cooke and Bliss, 2006). Thus, the NMDA receptor is a ‘detector’ for presynaptic and postsynaptic depolarisation which allows LTP to follow Hebbian principles (Bliss and Richter-Levin, 2004). The influx of Ca^{2+} ions activate calcium-sensitive signalling mechanisms, such as the enzyme calcium/calmodulin dependent kinase II (CaMKII) or the cyclic adenosine monophosphate (cAMP)-dependent pathways (Cooke and Bliss, 2006). These molecules initialise the LTP expression mechanisms where they phosphorylate receptors and change the intrinsic properties of the ion channels, send signals to the cell nucleus via transcription factors to modify gene expression (Goelet et al., 1986, Alberini et al., 1995). This increase in synaptic activity and post-synaptic excitability i.e. LTP is enhanced when applying high-frequency stimulation to the motor cortex (Hess and Donoghue, 1994, Hess and Donoghue, 1996, Hess, 2004).

2.3.3 Neuroplasticity and Long-Term Depression

High frequency results in LTP however low frequency induces depression of activity, termed as Long-term Depression (LTD) (Staubli and Lynch, 1990). This involves two processes. First, the cell reverses the effects of LTP or secondly by lowering levels of post-synaptic calcium concentration in relation to the

NMDA receptor (Cooke and Bliss, 2006). Second, LTD could also be linked to the reduction of *gamma*-Aminobutyric acid (GABA) receptor efficiency which is the main inhibitory neurotransmitter (Bliss and Collingridge, 1993). Neuroplasticity involves changes at the synapse level which could result in an enhanced activity of the inhibitory interneuron. This masks the cortical pathway whilst a reduction in activity of the same neuron can unmask the pathway (Harvey and Stinear, 2010).

2.3.4 Structural plasticity and metaplasticity

During neuroplasticity, changes occur at cellular level, however, it has been speculated that unmasking of silent synapses can also occur (Ward et al., 2006) in addition with formation of new synapses (Geinisman et al., 2004). Disproving the theory that neurons are not formed at cortical level, neurogenesis has shown to occur at the striatum, neocortex and amygdala (Gould et al., 1991, Magavi et al., 2000, Dayer et al., 2005). However, the occurrence has been a controversial topic and disproved by Bhardwaj et al. (2006).

It has been speculated that there are consequences to the LTP and LTD. Bienenstock et al. (1982) demonstrated that synapses working in a Hebbian fashion might result in maximally saturated via LTP or desaturated via LTD. As a result, they suggested the Bienenstock, Cooper, and Munro (BCM) learning rule: a large induction of synaptic activity makes LTP more difficult to induce and LTD is easier to induce with decreased synaptic activity (Wexler and Stanton, 1993). A negative feedback is developed to prevent this with a sliding action during periods of high synaptic activity. Thus, this BCM rule follows into another phenomenon, ‘metaplasticity’, which refers to the plasticity of the synaptic plasticity (Abraham and Bear, 1996). This occurs in various regions of the cortex including the motor area (Rioult-Pedotti et al., 2000, Harms et al., 2008). When then there is a sliding action of favouring LTP or LTD, a homeostatic mechanism shifts the level to back to the physiological range and this is termed homeostatic plasticity. These changes are related to changes in post-synaptic ion channels and post-synaptic glutamate receptors (Leslie et al., 2001, Davis, 2006).

Neuroplasticity is also modulated by a group of chemicals called neuromodulators (Stagg and Nitsche, 2011). Noradrenaline, dopamine and acetylcholine are such neuromodulators that potentially enhance synaptic plasticity in various cortical regions (Kirkwood et al., 1999, Blond et al., 2002, Ge and Dani, 2005). The brain-derived neurotrophic factor (BDNF), a neutrophin, has been shown to also influence Hebbian plasticity and this homeostatic process (Leslie et al., 2001, Copi et al., 2005). BDNF has an effect on the post-synaptic receptors and induce LTP without any neuronal stimulation and also seems to occur after Non-Invasive Brain Stimulation (NIBS) and this is discussed in section 2.5 (Pang and Lu, 2004, Bekinschtein et al., 2008).

2.3.5 Neuroplasticity and stroke

Neuroplastic changes can occur in healthy people (Classen et al., 1998), in animals and humans with a damaged motor cortex (Nudo et al., 1996a, Nudo et al., 1996b). Functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography have illustrated damage to cortico-spinal tracts leading to the malfunctioning of the primary motor cortex following an ischaemic stroke. However, the injured brain is also highly plastic especially during the early stages. In fact, in 2005 it was shown that neuronal growth-promoting genes such as GAP-43 (growth-associated protein 43) are expressed during the first week after ischemic injury (Carmichael et al., 2005). In stroke, neuroplasticity occurs at synaptic level and also at axonal and dendritic level. Sprouting occurs at the axons and dendrites in contra- and ipsi-lesional regions as found in animal models (Carmichael et al., 2001). However, brain structures gradually reduce ability to reorganise over time (Nudo et al., 1996a, Qü et al., 1998) although functional plasticity could be achieved at any time after stroke (Schaechter, 2004, Ward, 2005, Schaechter et al., 2006). This eventually results in an enhanced activation of the secondary motor areas such as the supplementary motor area, the dorsolateral premotor cortex and also the contra-lesional hemisphere (Ward and Cohen, 2004b).

2.3.5.1 Inter-hemispheric Inhibition

Maladaptive neuroplasticity in stroke could sometimes hinder motor recovery due to inter-hemispheric inhibition. Imaging studies have reported that for motor recovery to occur, there is also activity at distant sites such as the premotor cortex (Frost et al., 2003) or the contralateral hemisphere (Biernaskie et al., 2005). Recent fMRI images have demonstrated that when the affected UL is moved, both motor areas of the cortex are activated after stroke (Weiller et al., 1992, Calautti and Baron, 2003). This is due to transcollosal inhibitory connections leading to an enhanced inhibitory drive from the unaffected motor cortex to the affected motor cortex in stroke (Liepert et al., 2001a, Liepert et al., 2001, Murase et al., 2004, Nowak et al., 2009).

This inter-hemispheric imbalance has been found to be greater in people with stroke with a poorer recovery (Ward et al., 2003a, Ward et al., 2003b). As opposed to a sub-cortical stroke, the Gamma-aminobutyric acid (GABA)-ergic intra-cortical inhibition is suppressed after a cortical stroke which could be associated with enhanced glutamatergic activity (Que et al., 1999). In fact, recovery after a cortical stroke is often more difficult to achieve compared to a sub-cortical stroke (Hesse et al., 2007). Moreover, participants in the chronic stage (n=9) with poor functional recovery showed an increased inter-hemispheric inhibition (Murase et al., 2004). One could also reduce this inhibition by using cortical stimulation (Wittenberg et al., 2007). However, the disinhibition of intra-cortical inhibition in the sub-acute stage may be not enough to stimulate homeostatic plasticity and this could be different according to the location of the stroke (Kim et al., 2009). Additionally, researchers have debated whether the increased activity in the contra-lesional motor and premotor cortex acts a form of adaption (Johansen-Berg et al., 2002, Lotze et al., 2006).

Neuroplasticity involves cortical and sub-cortical structural changes which is essential for stroke rehabilitation. However, creating an enriched environment is also a driver of neuroplasticity in stroke which has also been demonstrated in rats (Johansson and Ohlsson, 1996). In addition, to a stimulating environment, repetition and education can also lead to motor learning and recovery (Albert and Kesselring, 2012).

2.3.6 Motor learning and skill acquisition

Motor learning has been defined as “a set of processes associated with practice or experience leading to relatively permanent changes in the capability for movement” (Schmidt, 1988). Motor learning involves a neural network in various areas of the brain including premotor, primary motor and supplementary motor cortices, the cerebellum, thalamic nuclei and the striatum (Grafton et al., 1998, Honda et al., 1998, Nezafat et al., 2001, Ungerleider et al., 2002).

Humans have the capacity to plan, learn and retain new motor skills which are essential for carrying out daily activities such as playing a sport or driving (Tanaka et al., 2011). In people with neurological injury, skill reacquisition depends on the capacity for recovery of function. People with stroke who have motor impairments need to relearn the motor programmes used prior to the brain lesion. This depends on the type of brain lesion, volume, location and the remaining functioning motor tracks and results in a complex process of motor recovery (Nowak et al., 2009).

2.3.7 Learning new motor skills

The primary motor cortex is an important part of the brain and neural network involved in the process of skill acquisition (Karni et al., 1995). However, reaching for a mug or reading are both different skills and therefore, involve different pathophysiological mechanisms (Tanaka et al., 2011). Skill is the capability of carrying out a task such as lifting a cup from the table to the mouth, with efficiency and fluency (Harvey and Stinear, 2010).

Skill acquisition can be fast over a single training session but then slow over multiple training sessions (Doyon and Benali, 2005). Learning has been associated with enhanced synaptic connections until it reaches asymptotic levels (Buonomano and Merzenich, 1998, Dayan and Cohen, 2011). In addition, acquiring a new motor skill involves the gain of motor synergies and new movement qualities that improves performance (Reis et al., 2008). Learning can occur during the training session (online) but also after the training has ended (offline) (Dayan and Cohen, 2011).

Consolidation or off-line improvements occur whilst someone is awake or sleeping (Walker et al., 2003, Stickgold, 2005, Marshall and Born, 2007). If the person is aware of the underlying sequence then off-line improvements occur during sleeping. If the person is unaware, then improvements can occur while awake or sleeping. However, during motor learning of a task, consolidation also occurs which include off-line improvements but also stabilisation. The latter refers to maintenance of the practice-induced skill. One must not forget to mention that, skill training also requires the person's ability to integrate motivation with the motor relearning process (Harvey and Stinear, 2010).

Fast and slow skill learning induces different neuroplastic changes such as in synaptic efficacy, dendritic branching and cortical representation (Kleim et al., 2004, Kleim et al., 1996, Dayan and Cohen, 2011). This occurs with a rebalance of inhibitory and excitatory connections linked with LTP and LTD (Harvey and Stinear, 2010). Massed and focussed practice during rehabilitation results in learning motor skills and changes in the motor cortex (Elbert et al., 1995, Nudo et al., 1996b, Liepert et al., 2001a).

2.3.8 Rehabilitation and learning new skills in stroke

The main goal of rehabilitation is to regain physical, psychological, social functions and also improve the quality of life of stroke individuals with various motor, sensory and cognitive impairments (Wang et al., 2010). Consequently, neurological rehabilitation can be considered multimodal. It improves function, activity and participation which can be targeted through goal-setting (Albert and Kesselring, 2012).

Rehabilitation techniques are used to promote cortical re-organisation involving anatomical and physiological changes (Dobkin and Dorsch, 2013). This re-organisation results in learning new skills and thus motor recovery. This enhances functional cortical reorganisation in the sensorimotor cortex of the affected hemisphere (Cramer et al., 2002, Johansen-Berg et al., 2002, Jang et al., 2004). Dynamic neural motor substrates which are made up of hard-wired motor networks could be remodelled or unmasked by motor practice (Nudo et al., 1996b, Toni et al., 1998, Ziemann et al., 2001). Such motor practice could include techniques such as Constraint Induced Movement Therapy (CIMT) or RT which are currently being used as part of UL rehabilitation research programmes for people with stroke (Tanaka et al., 2011).

2.3.9 Rehabilitation of upper limb impairments after stroke

As previously mentioned, advanced acute treatment such as including thrombolysis has reduced the mortality rate. However, this has not altered the level of rehabilitation needed in stroke. Multidisciplinary rehabilitation is one of the most important influences on motor improvements at any time post-stroke (Albert and Kesselring, 2012, Dobkin and Dorsch, 2013). Neurological rehabilitation for people with stroke is usually based on various techniques such as the Bobath, 'neurodevelopmental' concept (Dickstein et al., 1986, Bobath, 1990, Kwakkel et al., 2004a). However, there is a lack of evidence showing whether this concept used in rehabilitation is superior over other treatment programmes at improving UL impairments (Paci, 2003, Luke et al., 2004a, Kollen et al., 2009).

The Bobath concept mainly focusses on teaching people how to normalise movement and tone (Krakauer, 2006). However, this concept lacks any scientific evidence. As a result, in the past 15 years, scientific evidence has emerged that the neurological system has the potential to recover as discussed in the previous section (Nudo et al., 1996a). Strong evidence supports the fact that task-oriented rehabilitation training can stimulate the natural pattern of functional recovery. This supports the view that recovery can be encouraged by adaptive strategies that compensate for impaired body functions (Kwakkel et al., 2004a, Murphy and Corbett, 2009, Levin et al., 2009). In addition, there seems to be a different trend of recovery between people in the sub-acute and chronic stage of a stroke due to different phases of neuroplasticity and level of motor activity (Albert and Kesselring, 2012).

In the first few hours and weeks after a stroke, natural recovery involves a decrease in local oedema and resolution of diaschisis of areas of metabolically depressed cortical tissue (Teasell et al., 2005). It involves a combination of spontaneous and learning-dependent processes involving restoration of damaged neural tissue by restitution (Kwakkel et al., 2004a). This is followed by reorganisation of partly spared neural pathways to relearn lost functions by substitution and improvement of impaired skills in relation of the environment by compensation. Evidence suggests that improvements in motor function occur mainly in the first three months post-stroke (Traversa et al., 2000). Langhorne et al. (2011) explored UL recovery emphasising that during the first month there is most potential for UL recovery (Figure 2.4).

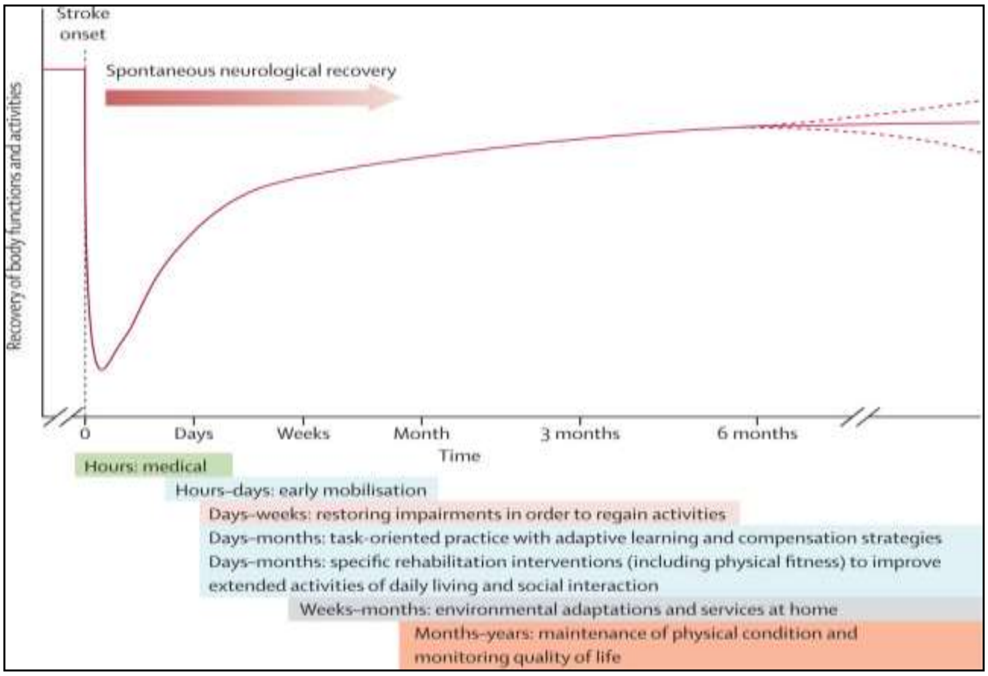

Figure 2.4 Hypothetical pattern of recovery after stroke

Colour green referring to pathology; light blue referring to activities; purple to body function and impairments and red to participation of WHO model(Langhorne et al. 2011)

The first six to twelve weeks is the best time for enhancing neuroplasticity in the brain after a stroke (Ward and Cohen, 2004a, Murphy and Corbett, 2009). It can be observed that this recovery might reach a 'plateau' after three months (Figure 2.4). This 'plateau' has been debated in literature since research also indicates that recovery can still occur many years' post-stroke (Demain et al., 2006, Schaechter et al., 2006, Wolf et al., 2006, Lo et al., 2010, Ferrarello et al., 2011). This is in conflict however, with the findings from a review and meta-analysis which concluded that there was inconclusive evidence that therapy-based rehabilitation one year post-stroke was able to influence any relevant patient or carer outcome (Aziz et al., 2008).

2.3.9.1 Factors influencing UL motor recovery and rehabilitation in stroke

Certain principles are relevant to stroke rehabilitation outcome, one of them being 'use it or lose it' (Kleim and Jones, 2008). If the brain is not stimulated due to lack of use it may lead to further disability. Another principle is 'specificity'. Including a specific rehabilitation technique can result in specific synaptic and motor map changes (Kleim et al., 1998). In unimpaired people, motor learning has been more prone to occur if a task involved increased practice (Lee et al., 1992). Following stroke, recovery of sensory-motor control also requires repetition, needs to be task-specific and carried out immediately after the stroke and also needs to be intensive.

Repetitive movement during rehabilitation of the UL can result in gaining functional outcome due to relearning or newly learned behaviour (Bütefisch et al., 1995, Kleim and Jones, 2008). Research involving the study of neurophysiology in mammals has demonstrated that repetition is the foundation for motor recovery and learning (Asanuma and Pavlides, 1997). In rats, a reaching task did not lead to modulation of synaptic strength until several days of training was carried out (Monfils and Teskey, 2004). Additionally, a task-specific “motor relearning program” which focuses on skill acquisition has also been shown to be more effective on increased level of independence during ADLs and on motor recovery compared to other approaches such as Bobath (Langhammer and Stanghelle, 2000). In addition to being repetitive and task-specific, rehabilitation should also start as soon as possible after the stroke (Bernhardt et al., 2009).

Another principle is that ‘time matters’. Early mobilisation leads to increased rate of discharge and lowers level of disability (Indredavik et al., 1999). In early stroke rehabilitation, functional improvements are generally noticed after 25 hours of motor retraining (Oujamaa et al., 2009). Animal studies have shown that during the first three weeks neuronal sprouting and increased growth-promoting factors occurred after training (Biernaskie et al., 2005, Murphy and Corbett, 2009). From a meta-analysis study, a high significant correlation has been found between immediate provision of neurological rehabilitation and functional recovery in a large study involving 969 people with stroke (Jette et al., 2005). Time delays between the provision of rehabilitation and the first day of stroke can also promote unnecessary compensatory behaviours that might result in poor movement quality (Kleim and Jones, 2008). Apart from immediate initiation of rehabilitation, intensity is also essential for motor recovery (Kwakkel et al., 2004b, Saunders et al., 2004).

Clinical studies show that starting rehabilitation as soon as possible after a stroke and high intensive therapy leads to a better outcome. Animal studies have shown that skilled reaching tasks carried out 400 times a day resulted in a greater number of synaptic connections in the motor cortex than if the tasks were carried out 60 times a day (Luke et al., 2004b, Kleim et al., 2002). In a randomised controlled trial involving 49 participants with sub-acute stroke (seven weeks post-stroke), the group receiving intensive UL therapy led to significant reduction of UL impairments and improvement of UL dexterity compared to non-significance in the conventional therapy group (Shimodozono et al., 2013). However, overuse of the impaired UL in the first two weeks can potentially lead to poorer recovery (Humm et al., 1998). The lack of definitive evidence may be due to the majority of research being conducted on animals (Langhorne et al., 2011). Further research exploring the mechanisms that drive recovery of disabilities and impairments involving humans is required.

2.3.10 Summary of neuroplasticity and upper limb recovery after stroke

Neuroplasticity occurs at synaptic level resulting from changes in the connections in the nervous system. This depends on various influences from the environment. In unimpaired and impaired individuals motor learning occurs due to neuroplasticity. After stroke, rehabilitation can promote motor learning and recovery. The sensorimotor recovery depends on influential factors such as time, task-specificity, repetition and also the intensity. RT can give a substantial contribution to all these factors for UL motor recovery after stroke.

2.4 Behavioural training- Robot therapy

The following section is about new approaches used for motor recovery following stroke and how these techniques build on the current understanding of neuroplasticity. This section also reviews the basic science and evidence specifically on RT and subsequently on NIBS.

Intensive, varied and goal orientated practice is associated with enhanced motor learning (Kwakkel et al., 2002). Physical therapy can provide such practice, but is resource expensive and standard rehabilitation does not always provide the frequency and intensity needed for motor learning (Sivan et al., 2011). Robot-assisted therapy has the potential to address some of these issues and could be used in an UL stroke rehabilitation programme.

2.4.1 Rehabilitation robots

Robots have been defined as a ‘machine’ which is designed to function in place of a living agent and carries out a variety of tasks automatically (Čapek and Novack, 2004). Several robots have been developed to promote UL movement and rehabilitation (Riener et al., 2005). In fact, robot machines have been chosen to promote labour-intensive training paradigms, provide a new tool for rehabilitation specialists and motivate stroke survivors’ access to therapy (Loureiro et al., 2011).

Rehabilitation robots can either be passive or active. There are various types of robots however most are either end-effector or exoskeleton-based systems.

Figure 2.5 End-effector robot: MIT-Manus® Robot

The end-effector robot involves a system interacting with the patient using a single distal attachment on forearm as an orthosis (e.g. MIT-Manus®) (Figure 2.5). The exo-skeleton robot encapsulates the arm and has the ability to control the orientation of the arm (e.g. Armeo®Spring) (Figure 2.6).

Figure 2.6 Exo-skeleton robot: Armeo®Spring robot

(Image courtesy of Hocome AG)

The latter robots can be either two-dimensional or three-dimensional and can have haptic and/or virtual reality systems. The latter systems have shown to increase motivation whilst carrying out exercise programmes by individuals with stroke (Loureiro et al., 2011).

2.4.2 Robot therapy

RT emerged in the 1990's as a promising intervention for rehabilitation of impairments experienced by people with stroke (Fasoli et al., 2003, Hesse et al., 2003). Dijkers et al. (1991) were the first clinical researchers to accept RT as a repetitive movement during occupational therapy for therapists and patients. Subsequently, researchers at Massachusetts Institute of Technology, decided to integrate Dijkers's idea in stroke rehabilitation (Hogan et al., 1992). Robotic devices can provide external assistance and, thus, can potentially improve the quality of rehabilitation strategies for people with stroke (Lum et al., 2002). A robot should simulate human-therapist behaviour i.e. it should assist the correct movement, increase patient's confidence and motivation levels through goal-orientated biofeedback and appropriate support. This could be linked with reward-related motor learning by means of dopamine (Wickens et al., 2003).The health care professional can also record the individual's progress by data processing and analysis (Loureiro et al., 2011).

Repetitive robot-assisted movements can be performed at a high intensity with minimal or no supervision, leading to improved motor ability and functional performance (Hsieh et al., 2011, Miller et al., 2010). Additionally, performance during robot training might be improved by providing visual feedback and also integrating force and kinematic measures.

Robots have been developed for either uni-lateral or bilateral arm training. Bilateral arm training is important because daily activities such as dressing or bathing involve use of both ULs (Waller and Whitall, 2008). The supplementary motor area has been linked with bilateral arm movements however the neurons activated are different to the ones activated during unilateral arm movements (Donchin et al., 1998, Kazennikov et al., 1999). Bilateral training has not been found to be superior over the unilateral training groups (Platz et al., 2001). Uni-lateral training has shown to promote re-organisation of the ipsi-lesional and contra-lesional cortices (Liepert et al., 2000, Johansen-Berg et al., 2002, Jang et al., 2003, Lewisand and Byblow, 2004). Use of both techniques has resulted in improvements of UL movements in people with stroke (dependent on the level of UL severity). In a review of bilateral training it was concluded that unilateral paretic UL function post stroke could be improved, however, specific training regimes require matching to the baseline level of ability of the patients (Waller and Whitall, 2008). Additionally the review recommended that research including bilateral training should involve assessments of bilateral functioning. Therefore, one cannot conclude which is the better option in stroke rehabilitation.

Robotic devices are expensive however, they can reduce the capital expenditure due to increased efficiency of therapists' current practice and can be used to treat a large number of patients (Lum et al., 2002). Currently in the UK, the Stroke Guidelines recommend that RT should only be used as an adjunct to conventional therapy when the main goal of the person with stroke is to minimise arm impairment or in the context of a clinical trial (Royal College of Physicians, 2012). RT is currently seen as an adjunct not a replacement to physiotherapy, with clinical decision making resting with the therapist (Loureiro et al., 2011). RT is seen to have potential to reduce the burden on clinicians and the healthcare systems (Lu et al., 2011b). A recent questionnaire study carried out in the UK showed that only 2% of the health care professionals and people with stroke have used RT in clinical practice which was due to several factors and which is further discussed in the next section (Hughes et al., 2013).

2.4.3 Views and perspectives of professionals and users about robot therapy

Quantitative research refers to the acquisition of quantities or quantifiable data (objective) properties such as randomised controlled trials and questionnaires. Qualitative research apparent qualities are collected such as views and experiences-. The aim of employing a qualitative approach was to provide an in-depth level of insight into a specific area through directly exploring people's beliefs and opinions (Flick, 2009). Qualitative research is not concerned with finding a 'fixed truth' and generalising the findings to the wider population, but aims to understand and interpret the main issues presented.

Physiotherapists' perspectives regarding rehabilitation robots were primarily explored by Lee et al. (2005). From the survey, it was concluded that acceptance of rehabilitation robots has been difficult due to the cost, size and lack of adaptation to the patient impairments. However, this study had a small sample size (n=17). A larger survey involving 233 respondents (physiotherapists) from Australia, Canada and United States of America was administered in order to explore the views about current stroke rehabilitation methods and aims and also asked for the desirable features of UL rehabilitation (Lu et al., 2011a). The main features required for a robot expressed by the participants were the following: being usable while seated, facilitating varied arm movements, giving biofeedback to clients, in combination with virtual activities specific to daily living, useful at home and adjustable to client's needs and finally that the robot should cost less than 6000 Dollars (approximately 4,000 British pounds). These findings must be viewed with some caution due to the limited geographic location of the respondents.

A recent questionnaire study carried out by Hughes et al. (2013) explored the perceptions of 123 people with stroke and carers and 292 health care professionals about the barriers and opportunities about assistive technologies including RT into stroke rehabilitation in the UK. All the health care professionals viewed robots as durable, fun to use and evidence based. However, they felt that robots cannot be used at the patients' home and were not good value for money. However, smaller robots are now available that can be used in the home of people of with stroke. Participants with stroke did not respond any of the aforementioned features in the RT section. This could be due to the lack of current use of RT in clinical practice.

Views and perspectives about assistive technologies from participants from the same population of the aforementioned study were also obtained using an in-depth qualitative method involving focus groups (Demain et al., 2013). People with stroke agreed that there is a motivational aspect for assistive technologies and the fact that RT was 'hi-tech' resulted in the rehabilitation being more enjoyable than standard rehabilitation techniques. They also stated that they did not have access to information about assistive technologies and hence why most of the people with stroke did not respond to any questions about RT in the aforementioned study. They participants also suggested that technologies should be used at home however, lack of funding is still a problem.

A system combining robots with functional electrical stimulation has been developed taking into account users' perspectives development. The first study explored the perceptions of five participants with chronic stroke about factors such as usability and effectiveness of RT by asking them several questions (Hughes et al., 2011). The participants agreed that the system was usable, that their arm felt stronger and gave them the ability to pick up objects. However, they had opposing perceptions on the effect of RT on arm awareness and tightness, and ease of reach after RT. This resulted in a change in the system and a further trial. Semi-structured interviews were then carried out with five participants with chronic stroke (Meadmore et al., 2014). They also thought the system was useful and improved their UL impairments but they still felt they could not use their UL functionally.

Therefore, in conclusion participants with stroke think that RT is enjoyable and provides motivation during rehabilitation. RT can improve UL impairments although it might not result in changes in UL function. Health care professionals agreed with the aforementioned aspects however felt there is a lack of funding to provide such assistive technologies in health care settings. Therefore, RT should be cheap and also adjustable to home-use.

2.4.4 Review of RT targeting UL impairments and function

Uni-lateral and bilateral RT has been shown to improve chronic motor impairments in people with moderate to severe UL dysfunction after stroke (Fasoli et al., 2003). RT can also result in greater improvement in moderate and severe UL motor impairments for both sub-acute and chronic stroke survivors compared to conventional therapy (Volpe et al., 1999, Fasoli et al., 2003, Fasoli et al., 2004, Liao et al., 2012).

Lo et al. (2010) carried out the largest RCT to date involving RT and 127 participants with chronic stroke with moderate to severe UL impairments. The trial consisted of three groups; (1) intensive RT (36 sessions over 12 weeks), (2) intensive comparison therapy and (3) usual care. The robot had four modules: shoulder-elbow, anti-gravity, wrist and a hand unit and movements were directed by videos. The intensive comparison therapy involved the same amount of sessions and followed an exercise programme. The results did not show any significant differences in motor impairments between the first and second and third groups (p=0.08, p=0.92 respectively). The participants in the first group showed a 2.17 point difference compared to the third group. Significant differences were found in social participation between RT and usual care group (p=0.009) however non-significant between the first and second group (p=0.81). No significant changes were reported for the UL dexterity and speed of movement in all groups. At follow-up, participants receiving RT showed a significantly better motor impairment and dexterity score (p=0.02) than those receiving usual care. However, still no significant differences between group one and two (p=0.63). Thus, highly repetitive and intensive therapy is the way forward for UL recovery. In this study, the chronic participants had moderate to severe UL impairments and so the results are not generalisable to people in the acute/sub-acute stages, or those with mild UL impairments.

Kwakkel et al. (2008) reviewed the overall effects of robot-assisted therapy on UL recovery after stroke. The authors concluded that RT resulted in significant improvements in UL function but not in ADLs. They stated that improvements in motor function of the UL occurred at the shoulder-elbow level but not at the wrist-hand level which could be due to inappropriate choice of tools to measure dexterity of the arm. The researchers recommended that tools measuring function at all regions of the arm such as Action Research Arm Test (ARAT) should be used in future trials. The authors also concluded that larger trials with the appropriate choice of outcome measures were needed. Subsequently, Sivan et al. (2011) carried out a review exploring which outcome measures would be ideal for the evaluation of effects of RT on the UL in stroke. The review concluded that the choice of outcome measures should cover all domains of the ICF. In addition, the choice of outcome measures should be based on the protocol such as severity of UL impairments, time since stroke and intervention.

Norouzi-Gheidari et al. (2012) conducted a systematic review and meta-analysis exploring the effects of RT on UL rehabilitation in stroke. With 12 studies included in the review, the researchers explored whether RT compared to conventional therapy leads to significant improvement ($p=0.01$) in UL impairments and functional ability. They concluded that when the duration/intensity of conventional rehabilitative therapy was matched with that of RT, no statistically significant difference ($p=0.28$) was demonstrated in FMA (motor impairment scale) scores between the two groups. However, it was reported that when RT was used an additional therapy the effect was significantly higher ($p=0.004$). It would have also been interesting if the researchers compared the effect of bilateral with unilateral RT on UL impairments and function of people with stroke. Limitations of the study were that significant levels were reported rather than effect sizes.

Mehrholz et al. (2012) also explored the effectiveness of electromechanical and robot arm training for improving generic activities of daily living, arm function, and arm muscle strength in patients after stroke in their Cochrane review and meta-analysis. They included 19 trials and they showed that the intervention does improve activities of daily living and arm function with a significant positive effect size of 0.43-0.45. From their sub-group analysis they noted that that robot arm training improves ADLs in the acute phase but not during the chronic phase of the stroke. Potential limitation of this review is that the studies included involved bilateral and unilateral RT which might lead to different UL improvements.

This section explored how an assistive technology such as RT for the impaired UL can be integrated in stroke rehabilitation. Evidence shows that RT results in better UL impairment and reduction in stroke impact compared to usual care. In addition, there is evidence that RT results in better UL improvements when added with other rehabilitation programmes and technologies. Thus, the following section discusses how NIBS can be added as an adjunct intervention with RT for UL motor recovery.

2.5 Non-invasive brain stimulation

It has been discussed that the intensity factor involved RT improves motor impairments of the UL. Recently, neurological research has been focussed on an alternative method of improving capacity of motor relearning. Inputting a current within the motor cortex could promote effective synaptic changes during task and skill focussed learning (Harvey and Stinear, 2010). Brain stimulation techniques in animal models resulted in Hebbian-like changes in cortical motor representation and synaptic activity (Nudo et al., 1990, Monfils et al., 2004). Squirrel monkeys with an induced stroke in their primary motor cortex, recovered quicker when they had a sub-threshold electrical stimulation in addition with rehabilitation for several weeks (Plautz et al., 2000). Therefore, recently robot-assisted therapy has also been combined with NIBS for the rehabilitation of UL impairments of people with stroke and has emerged as a promising health technology for neurological rehabilitation (Hesse et al., 2007, Edwards et al., 2009, Hesse et al., 2011).

NIBS is a method used to modulate brain function (Pascual-Leone et al., 2000, Paulus, 2003). NIBS can potentially lead to neuroplasticity and thus, motor recovery. There are various types of NIBS such as Transcranial Magnetic Stimulation (TMS) involving repetitive TMS (rTMS) or Theta-Burst Stimulation (TBS), Paired associative stimulation and transcranial Direct or Alternative Current Stimulation (tDCS/tACS) (Figure 2.7). The brain can also be stimulated invasively by techniques such as epidural cortical stimulation or deep brain stimulation. NIBS could be applied to increase excitability of the spared regions of affected motor cortex (anodal tDCS) or decrease excitability which is usually applied to the unaffected hemisphere (cathodal tDCS) (Fregni et al., 2005, Hummel et al., 2005, Mansur et al., 2005, Schlaug et al., 2008, Vines et al., 2008).

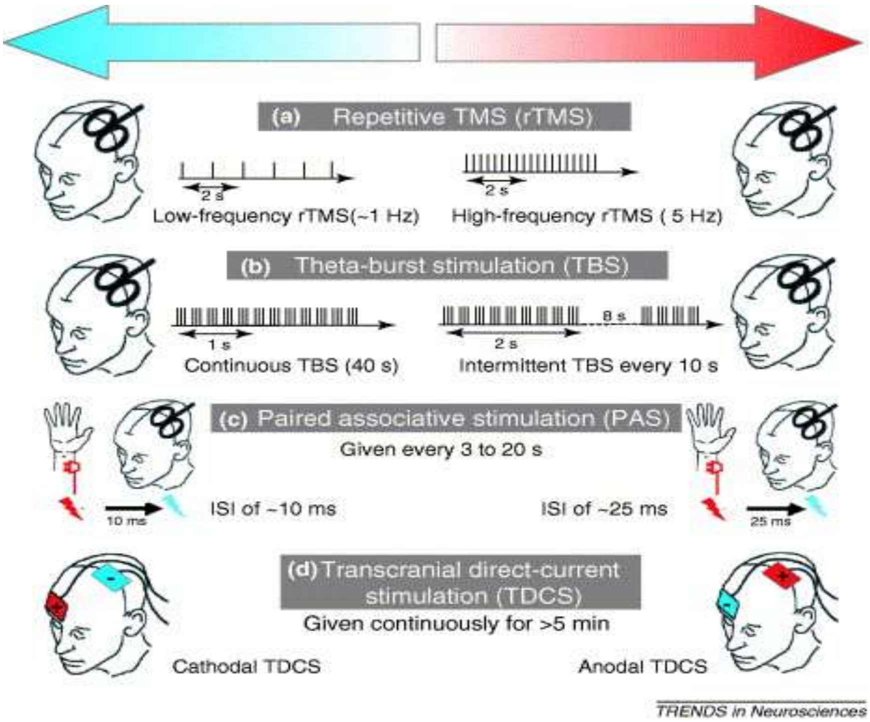

Figure 2.7 Different applications of non-invasive brain stimulation

Left side of the image displays the inhibitory form of NIBS and the right side displays the excitatory forms of NIBS(Quartarone et al., 2006)

Thus, NIBS can target the inter-hemispheric imbalance after stroke by down-regulating the unaffected hemisphere and disrupt the extra influence on the lesioned motor cortex (Nowak et al., 2009) (Figure 2.8).

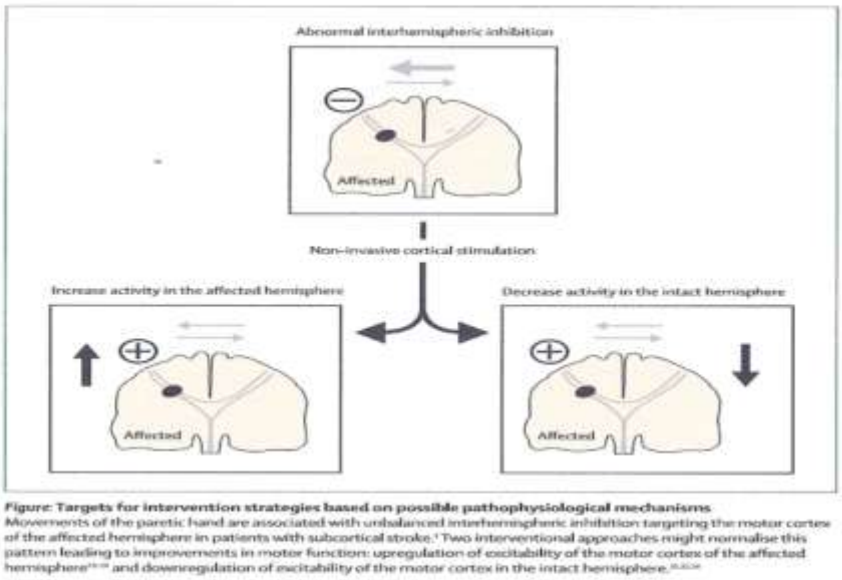

Figure 2.8 Application of non-invasive brain stimulation targeting maladaptive plasticity such as interhemispheric imbalance

(Hummel and Cohen, 2006)

In addition, application of bi-hemispheric stimulation using two magnetic coils or electrodes to stimulate both hemispheres at the same time is another form of application of NIBS (Vines et al., 2008, Lindenberg et al., 2010) (Figure 2.9).

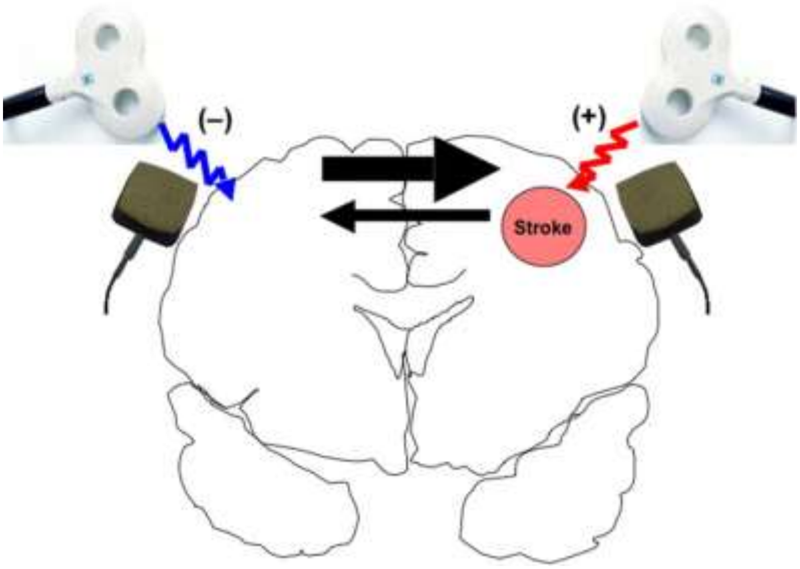

Figure 2.9 Example of bihemispheric stimulation

(Webster et al., 2006)

The two commonly used forms of NIBS (TMS and tDCS) have been described and the evidence for their clinical effectiveness is reviewed in the following sections.

2.5.1 Transcranial magnetic stimulation

TMS can be used as an assessment tool: diagnostic (Chen et al., 2008) or as a predictor of recovery or as an intervention tool by applying rTMS or TBS (Manganotti et al., 2012).

2.5.1.1 TMS and assessment

The principle behind TMS is Faraday's law of electromagnetic induction which states that a rapidly changing magnetic field induces a current flow in a nearby conductor. Through the use of a transducing coil attached to a high-voltage (400 volts to 3 kilovolts) and high-current (4kiloAmperes-20kiloAmperes) electric currents are induced by the magnetic field in the cortical tissue (Jalinous, 1991, Harvey and Stinear, 2010). The currents circulate up to few centimetres away from the coil's edge in a direction opposite to the current flowing in the coil whereby intensity is proportional to the magnetic field (Rossini & Rossi 1998). TMS applied to the motor cortex results in a flow of current in the top layers of brain tissue, activates intra-cortical interneurons which depolarises the membrane potential resulting in an action potential (Groppa et al., 2012). These interneurons then activate the pyramidal cells projecting to the spinal cord. If the motor cortex is stimulated, the spinal alpha motor neurons are activated i.e. the cortico-spinal tracts are activated (Rossini and Rossi, 1998). The increase in excitability is inferred from changes in amplitude of Motor Evoked Potential (MEPs). By applying a single pulse of TMS, a MEP of a muscle can be elicited (Figure 2.10).

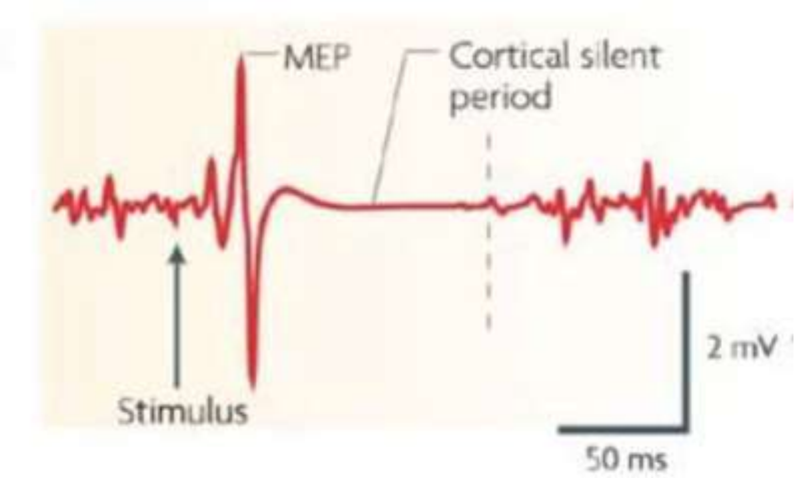

Figure 2.10 TMS stimulus eliciting a motor evoked potential followed by cortical silent period

MEPs can be measured during muscle contraction, which have larger amplitude and a shorter latency than if the MEP is measured when the muscle is at rest (Merton and Morton, 1980a, Merton and Morton, 1980b). The silent period can also be measured which is the inhibitory period in the cortico-spinal neurons after a MEP is elicited (Figure 2.10). If TMS is applied to the motor cortex and a MEP is not evoked, then that frequency was sub-threshold, however, if a MEP was induced greater than 50 microvolts (µV) then that is considered as supra-threshold (Rothwell et al., 1999). In the latter process, the changes in excitability in the motor cortex is descended to a summation at the spinal level to exceed the threshold of spinal motor neurons. The Resting Motor Threshold (RMT) is calculated as the intensity that evokes a MEP at 50 (µV) five times out of ten trials. These measurements can vary between different individuals especially people with neurological conditions such as stroke (Berardelli et al., 1987, Heald et al., 1993).

Single pulse TMS is a sensitive tool in identifying clinical impairments in people with stroke and is also able to identify subclinical abnormalities of the cortico-spinal pathway (Pennisi et al., 2002). In patients who are severely affected by a stroke, a MEP is difficult to be elicited however, people who are mildly affected by the stroke, a MEP is elicited but with small amplitudes and long latency (Rossini and Rossi, 1998). In fact, the presence of a MEP at the acute phase of stroke can be a good predictor of functional recovery of the UL (Cantano et al., 1996, Lee et al., 2010). TMS assessments have been used to understand the inhibitory and excitatory theories linked with the central motor system in acute and chronic stroke (Liepert et al., 2005). These involve motor thresholds, silent periods, motor cortical inhibition and facilitation and stimulus-response curves of unaffected and affected hemisphere. These types of assessments can determine the motor cortex activity in the ipsi- and contra- lesional hemisphere.

2.5.1.2 TMS and safety

In addition to TMS being a non-invasive method of modulating the excitability of motor pathways at cortical level, it is a safe procedure (Harvey and Stinear, 2010). Rossi et al. (2009) published a consensus report which described the following potential rare side effects of single-pulse TMS: seizure induction, syncope possible as epiphenomenon (i.e. not related to direct brain effect), transient headache, local pain, neck pain, toothache, paraesthesia, transient hearing changes. Induced currents in electrical circuits is theoretically possible but described malfunction only if TMS is delivered in close proximity with an electric device (e.g. pace-maker, brain stimulation, pumps, intra-cardiac lines, cochlear implants). Side-effects reported can be caused but very rarely after application of TMS. Still, participants with the latter conditions are usually excluded from TMS assessment and intervention.

2.5.2 Transcranial magnetic stimulation as an intervention

rTMS delivers trains of TMS pulses to the cortex however, unlike single pulse TMS, it results in cortical effects that outlast the period of stimulation and is thus therapeutic (Fitzgerald et al., 2006). TBS can be applied intermittently or continuously has also been used with people with stroke (Talelli et al., 2007, Di Lazzaro et al., 2008).

rTMS is safe and seizure occurrence have been reported in rare occasions (Yozbatiran et al., 2009). rTMS can modulate the cortical state in stroke (Mansur et al., 2005, Hummel and Cohen, 2006). High-frequency (5-20 Hertz [Hz]) can facilitate cortical excitability with effects lasting for 30-40 minutes (Pascual-Leone et al., 1998, Di Lazzaro et al., 2002, Peinemann et al., 2004) whilst low-frequency (<1 Hz) rTMS can inhibit the cortical excitability (Kobayashi et al., 2004, Théoret et al., 2004). rTMS could increase cortical excitability by improving the strength of some neural connections and synaptic transmission carried out by LTP (Pascual-Leone et al., 1994, Dinse et al., 1997, Lee et al., 2003, Siebner and Rothwell, 2003).

2.5.3 Transcranial direct current stimulation

Nitsche and Paulus (2000) demonstrated that weak, direct currents, applied transcranially, causes polarity-dependent changes in the cortex (Brunoni et al., 2011). It can modulate brain function depending on strength, duration of stimulation and polarity (Nitsche et al., 2005). tDCS is applied via saline-soaked sponge electrodes with a low voltage at a constant current stimulation at one to two milliAmperes (mA).

Anodal tDCS increases cortical excitability and cathodal tDCS decreases it (Boggio et al., 2007, Brunoni et al., 2012). This enhanced cortical excitability is significantly correlated with behavioural changes (Nitsche et al., 2002, Nitsche et al., 2005, Hummel et al., 2005, Hummel and Cohen, 2006). Unlike TMS, tDCS does not induce supra-threshold membrane depolarisation but changes neuronal network activity (Nitsche et al., 2008). In animal studies it has been demonstrated that an increased excitability occurs due to immediate spontaneous neuronal firing rates after tDCS (Bindman et al., 1964) which also occurs in humans (Priori et al., 1998).

The after-effects of the modulation of tDCS last to about one hour (Nitsche and Paulus, 2001, Nitsche et al., 2003b) and, therefore, neuroplastic changes are not only attributed to the change in electrical neuronal membrane i.e. activation of calcium- and sodium- dependant membrane channels, but also due to synaptic changes i.e. modification of the synaptic strength of NMDA receptors or altering GABAergic activation (Liebetanz et al., 2002, Wassermann and Grafman, 2005, Stagg et al., 2009). Therefore, tDCS can promote LTP and neuroplasticity (Fritsch et al., 2010). When the anode is placed over the motor cortex, partially depolarisation occurs resulting to an up regulation of NMDA receptors of the postsynaptic membranes whilst a down regulation of NMDA receptors with cathodal tDCS (Nitsche et al., 2003c, Nitsche et al., 2006). Additionally, tDCS has been shown to enhance Brain-Deprived Neurotrophic Factor (BDNF) secretion and tyrosine receptor kinase B activation in animal models, implying that tDCS may promote motor skill training through augmentation of synaptic plasticity and metaplasticity (Fritsch et al., 2010).

2.5.4 Safety and transcranial direct current stimulation

All tDCS studies carried out in humans since 1998 until 2008 were reviewed for safety aspects of tDCS (Nitsche et al., 2008). Thirty-one out of a total of 95 studies reported the following adverse reactions: itching under the electrodes, headache, tingling sensation under the electrodes, light flashes when current was turned on or off, redness of skin, sleepiness, mood changes, drowsiness, scalp burning, concentration problems (Gandiga et al., 2006). In a more recent study by Brunoni et al. (2011), 117 (56%) studies reported adverse reactions. The most common adverse reactions were: itching in 39.3% receiving real tDCS and 32.9% receiving sham tDCS, tingling in 22.2% receiving real tDCS and 18.3% receiving sham tDCS, headache in 14.8% reported for real tDCS and 16.2% reported for sham tDCS, burning sensation in 8.7% receiving real tDCS and10% receiving sham tDCS and discomfort in 10.4% receiving real tDCS and 13.4% receiving sham tDCS. The researchers of this study reported that selective reporting bias might have been presented in studies that reported sensations as mild adverse events after tDCS. Therefore, one needs to interpret these results with caution and appropriate and better quality reporting tools should be developed. In spite of this it is essential that adverse reactions need to be monitored during tDCS.

2.5.5 tDCS as an intervention

The three main reasons why clinical research involved tDCS in the past 12 years were because: a) tDCS is inexpensive b) tDCS can be a substitutive treatment for pharmacotherapy and finally c) tDCS can be used as an augmentative treatment such as stroke rehabilitation (Brunoni et al., 2012). tDCS has been used with various conditions such as depression with some positive results (Nitsche et al., 2009) however, evidence for its effectiveness in recovery of UL function in stroke is currently equivocal.

Earlier studies mainly explored the effect of one session of tDCS on UL function however, recent studies have shown that multiple sessions over two weeks can lead to better improvements in the UL after stroke however, this is not a linear response (Lindenberg et al., 2012).

2.5.5.1 tDCS for the UL in stroke

After 2005, researchers specialised in neurology started exploring the effects of tDCS on UL motor recovery. However, most of the studies included very small samples (n=5/6) of stroke participants. In addition, the studies involved a cross-over design and only involved one session of tDCS. These studies are discussed in detail in the next section.

2.5.5.2 Cathodal and anodal tDCS

The first stroke tDCS study explored the effects of the stimulation on the UL function in a cross-over sham controlled double-blinded study (Fregni et al., 2005). This study involved only six participants with chronic stroke receiving anodal stimulation on affected hemisphere, cathodal on the unaffected hemisphere and sham stimulation. This study explored the effect of one session of stimulation and evaluated UL activity using Jebson-Taylor Hand Function Test (JTT) clinical measure (assesses UL response time whilst carrying out hand functions required for activities of daily living), at baseline, during stimulation and twice post-stimulation. Both anodal and cathodal stimulation improved motor performance compared to sham stimulation. Therefore, from the first trial one can speculate that tDCS can improve UL function however, concrete conclusions can be made from a small sample.

In the same year, effect of anodal tDCS to the motor cortex of the affected hemisphere on the performance of motor tasks of also involved six people with chronic stroke was investigated (Hummel et al., 2005). The programme consisted of tDCS and behavioural testing, involving 2/3 sessions of real or sham tDCS over double-blinded cross-over trial. Each session included three measurements of response time using the UL measure JTT at baseline (JTT1, 2, 3), followed by a measurement during (JTT4), at 27 minutes post-intervention (JTT5 and 6) and at approximately ten days follow-up intervention (Figure 2.11).

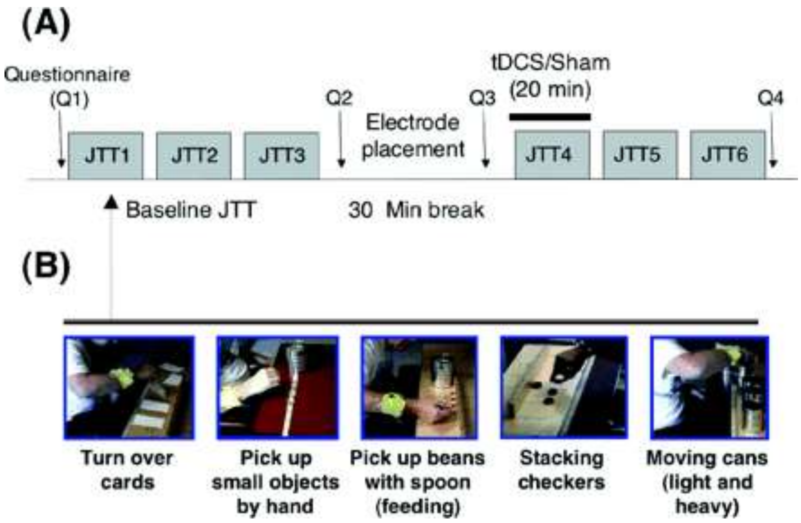

Figure 2.11 Experimental design by Hummel et al. (2005)

After post-hoc testing, it was shown that real anodal tDCS significantly reduced JTT response time (p=<0.05) relative to baseline compared to sham which outlasted the stimulation period for 25 minutes. A follow-up assessment showed improvements compared to the familiarisation sessions which returned back to normal after 10 days (Figure 2.12). Additionally, MEP recruitment curves were measured, post stimulation and at follow-up (25 minutes). These showed an overall increase in MEP recruitment curve slope after tDCS which correlated well with changes in JTT (r^2=0.78) in addition with reduced short-interval intracortical inhibition. Although this was a cross-over trial and involved a small sample, one key finding was that the after-effect of tDCS lasted for 25 minutes.

Two studies exploring the effects of (a) four weekly sessions of sham, anodal and cathodal tDCS and (b) five consecutive daily sessions of cathodal tDCS involving a small sample of nine people with chronic stroke were then carried out (Boggio et al., 2007). In the first study, four participants carried out an un-blinded cross-over trial and in the second study, five participants took part in the preliminary work. Motor function was evaluated using JTT clinical measure. A significant motor improvement after cathodal (p=0.034) and anodal stimulation (p=0.014) was demonstrated compared to sham stimulation in the first study. In the second experiment they showed a significant effect of time (p=<0.0001) on motor function after cathodal stimulation and the effects lasted for 2 weeks.

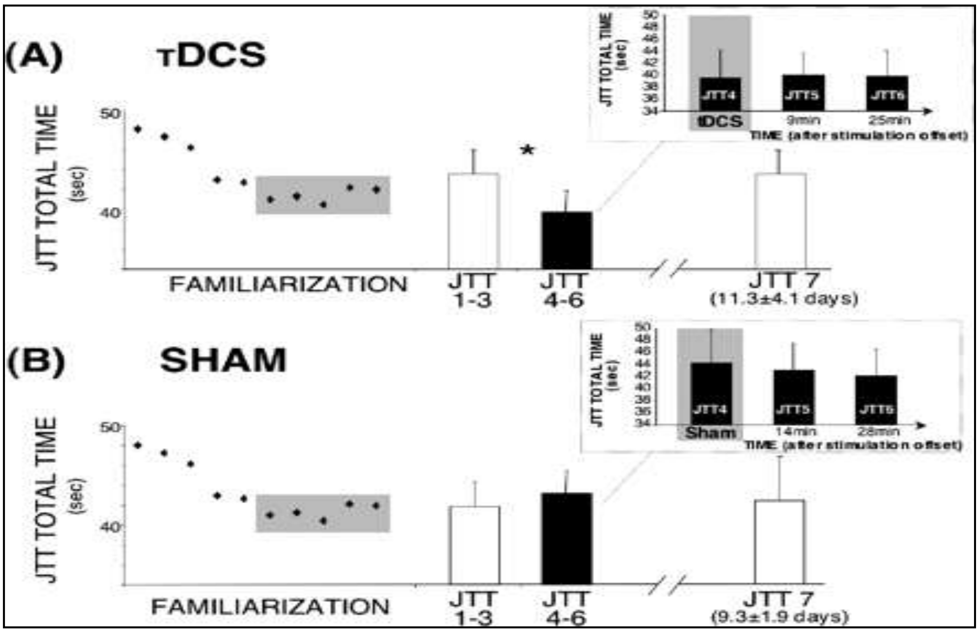

Figure 2.12 Results of the study by Hummel et al. (2005).

A significant decrease in reaction time by the UL is noted after anodal tDCS compared to sham stimulation.

Later in 2009, it was investigated whether anodal tDCS enhances motor performance of the paretic hand of people with sub-acute stroke in a single-blinded, sham-controlled, crossover study (Kim et al., 2009). The study involved 10 people with sub-acute stroke. Each participant had sham and active tDCS of the affected hemisphere. Box and Block Test (BBT), another UL function tool, did not differ between anodal and sham tDCS at baseline, however, repeated measures of analysis of variance revealed a significant interaction between the time factor and the intervention (tDCS and sham) at all-time points. The participants significantly improved (p=0.000) in the BBT immediately after tDCS compared with sham stimulation. In comparison with the baseline measurements there were also significant improvement (p=0.04) of BBT scores of the anodal group at 60 minutes post stimulation. This demonstrated that anodal tDCS resulted in enhanced motor performance in the paretic hand of people with sub-acute stroke which persisted even after 60 minutes of stimulation. The limitations of this study included a lack of detail on the type of stroke, the absence of neurophysiological measures, and the un-validated modification of the BBT.

The results from the aforementioned four studies indicate that tDCS has potential in improving UL impairments in chronic and sub-acute stroke. All the researchers used an intensity of 1mA and after effects of tDCS were maintained between 25-60 minutes, however, it must be noted that they involved small sample sizes, cross-over treatment and lacked blinding.

Even though NIBS has been shown to increase the development of neural connections involved in functional improvements, this type of technology fails to influence the brain with new knowledge in relation to skill acquisition (Malcolm et al. 2007). Thus, NIBS can be coupled up with rehabilitation to aim at enhancing skill acquisition.

2.5.6 tDCS and rehabilitation for the upper limb in stroke

In the past five years tDCS has been combined with other rehabilitation techniques such as RT, CIMT and OT. Different modes of tDCS were used in the different research studies and this is discussed in the following sections.

2.5.6.1 Bi-hemispheric tDCS and motor training

A single-blinded sham-controlled randomised trial investigated cortical excitability by applying bihemispheric tDCS on both motor cortices in combination with rehabilitation on motor outcome in 20 people with chronic stroke (Lindenberg et al., 2010). The study involved two groups (real or sham in addition with physiotherapy and occupational therapy). Stimulation was set at 1.5 mA for 30 minutes. The primary outcome measure was FMA (UL) and secondary outcome functional measures included Wolf Motor Function Test (WMFT) and a battery of motor activity tasks. Assessments were carried out three and seven days post-intervention. fMRI scans were recorded whilst the participants performed UL movements. Ssignificant improvements were found in FMA in the group receiving real tDCS ($Z=9.44$, $p=0.001$) and also receiving sham tDCS ($Z=5.92$, $p=0.001$) using linear mixed-effect regression and improvements lasted for a week. These findings were accompanied by functional changes in motor cortex activation. However, no comparison between the real and sham group was carried out in the study. In addition, the benefits of bi-hemispheric over uni-hemispheric stimulation are unknown and also the rationale for choosing an intensity of 1.5mA was not defined.

A double-blinded RCT was then carried out investigating the neurophysiological and behavioural effects of bi-hemispheric tDCS in addition with CIMT in 14 people with chronic stroke (Bolognini et al., 2011). Forty minutes of real or sham 2mA tDCS was delivered in addition with a 10 day CIMT programme. Clinical and neurophysiological measurements were carried out at baseline, half way through the intervention, at post-intervention and at two and four weeks follow-up. Significant improvements were demonstrated in the real group for the JTT and FMA measures compared to sham group (p=<0.01 both measures). With regard to JTT, the improvements remained stable at follow-up. Motor Activity Log (self-reported measurement of UL ADLs) was also used as an outcome measure and both groups improved significantly with time (p=<0.05) which remained stable at follow-up. The real group showed significant increase (p=<0.04) in peak to peak amplitude of MEP measured on affected hemisphere, however, no change in sham group. The effect of group and time was non-significant. Also, a positive correlation between cortical excitability in affected hemisphere and FMA score (r=0.67). One must note that the participants were not matched for functional severity and therefore, baseline measurements between the two groups are not comparable. However, after a year, from the aforementioned studies the intensity of tDCS was increased from 1mA to 1.5mA to 2mA without any justification.

2.5.6.2 Cathodal and anodal tDCS and motor training

In 2010, a prospective single-blinded RCT involving repeated sessions of 1mA anodal, cathodal and sham tDCS with occupational therapy programme involving 20 people with sub-acute stroke (Kim et al., 2010). Each treatment consisted of 10 sessions (5 times per week for 2 weeks) of 20 minutes each during OT sessions. UL motor function was assessed using FMA and Modified Barthel Index (MBI). Eighteen participants completed the study. The main effect of intervention with time was significant (p= 0.017) but the effect of the intervention alone was not significant (p= 0.537) on FMA scores. However, at post hoc analysis no significant differences in MBI (p=>0.05) were noted. FMA score was significantly higher (p=<0.05) after cathodal tDCS than after sham treatment at six months follow-up. The more severely affected participants (low score of FMA) benefitted more than the less severely affected participants (high score of FMA) (r= - 0.846). However, in the statistical analysis section, the researchers reported that they carried out one way analysis of variance which was then changed to two way analysis demonstrating inconsistency in the analyses.

The addition of cathodal tDCS with OT was also explored with 14 participants with chronic stroke in a double-blinded sham controlled trial (Nair et al., 2011). The study involved two groups receiving either sham or 1mA cathodal tDCS for 30 minutes during one OT. The study involved five daily sessions and assessments (FMA, Range of Motion and fMRI) were carried out at baseline and post-intervention. Significant differences were found favouring cathodal stimulation on FMA scores however, the post-intervention assessment was carried out a week after the end of the trial but the p-values was not presented. The sham showed a greater change of improvement at post-intervention than the cathodal group. A decrease in activation of the contralesional hemisphere was reported cathodal stimulation and they found this to be associated with better FMA scores. The results of the study are not clearly presented and the use of parametric tests was not justified.

The effect of cathodal tDCS on muscle tone and UL impairments in 90 participants between two to twelve months post-stroke in a double-blinded RCT was also explored (Wu et al., 2013). They included two groups of cathodal and sham tDCS for 20 minutes, five days a week for four weeks in addition with conventional PT. The period when stimulation was applied is not mentioned in this study. After the trial, a significant improvement ($p=<0.001$) was reported in the cathodal group compared to the sham group in spasticity measured by MAS. Significant differences were also reported in FMA and Barthel Index measures at post-intervention and follow-up for both groups ($p=<0.001$). The limitations for this study were that the outcome measure chosen to measure spasticity (MAS) is not a true measure of spasticity since it is very subjective and does not distinguish between muscle contracture and neurological properties of spasticity.

Khedr et al. (2013) carried out a pilot double-blinded RCT exploring the effect of anodal, cathodal and sham tDCS stimulation in addition with rehabilitation in people with sub-acute stroke. The treatment programme involved six daily sessions of 25 minutes of tDCS in addition with an exercise programme. Different outcome measures were used, National Institute of Health Stroke Scale. Orgogozo stroke scale and Barthel Index which measured severity and functional ability of stroke at baseline, post-intervention and at one, two and three months follow-up. A significant effect was reported for the anodal group versus sham (p=0.002) however marginal significant effect was reported in the cathodal group versus sham (p=0.017) for the Orgogozo stroke scale and Barthel Index but not for the National Institute of Health Stroke Scale. No effect was reported of real tDCS vs sham tDCS on RMT and active motor threshold on the un-affected hemisphere but significant for the affected hemisphere. A significant correlation was reported between the neurophysiological changes and the clinical scores for all the groups (r^2=0.37, p=0.001). Marginal significance for cathodal and sham groups (r^2=0.36 and 0.32, p=0.03 and p=0.04) but non-significance in the anodal group was also reported.

The aforementioned studies therefore showed that real tDCS had a significant effect on UL motor impairments and activities. All these studies involved conventional therapy methods for the UL. In fact, studies have also explored the effect of tDCS in addition with UL robot therapy and these will be discussed in the following section.

2.5.6.3 Cathodal and anodal tDCS in addition with RT

The effects of anodal tDCS with robotic wrist therapy in people with chronic stroke were explored in a small study involving six participants (familiar with RT) (Edwards et al., 2009). The intervention programme consisted of one session of 20 minutes of anodal tDCS (1mA) followed by one hour RT. MEP amplitude was measured at baseline, post-tDCS and post RT. Post tDCS, the MEP amplitude increased from baseline and remained increased after RT. Limitations of the study were that no clinical measures, blinding or randomisation were used. In addition, participants had already received an intense robot training programme before the study and therefore, one can debate that baseline assessments were not carried out at the right time.

A small pilot study involving 10 participants with sub-acute ischaemic stroke (8 had cortical and 2 had subcortical lesions) was also carried out involving bilateral robot-assisted arm training (Bi-Manu-Track) and tDCS (1mA) (Hesse et al., 2007). The protocol consisted of a six week arm training programme (every day 30 sessions), involving 20 minutes RT with seven minutes tDCS for each session. Two participants with sub-cortical stroke showed the most FMA improvement and a significant overall improvement ($p=0.018$) in FMA score in all participants. Interestingly, participants who had aphasia also improved in their communications skills after the treatment programme. Potential limitations included that this study did not involve a sham stimulation group and therefore results cannot be compared to the results of sham stimulation and RT.

After their pilot study in 2007, the same researchers carried out a double-blinded RCT which continued exploring the effects of combining tDCS and robot-assisted arm training on UL motor recovery with 96 people with sub-acute stroke (Hesse et al., 2011). This study involved three groups, receiving either 2mA (1) anodal or (2) cathodal or (3) sham stimulation for 20 minutes in addition with 20 minutes of RT using the Bi-Manu Track daily for six weeks. The participants continued receiving their standard rehabilitation four times a week for 45 minutes. Clinical assessments (FMA and BBT) were used at baseline, at post-intervention and at three months post-intervention. There were significant improvements ($p=<0.001$), in the FMA scores over time however, no group significant differences ($p= >0.025$) were found. Interestingly, within the cathodal group participants with a sub-cortical stroke significantly improved ($p=0.0014$) much more than those with a cortical stroke. The researchers argue that there is a possibility that a uni-lateral RT might produce a better effect between groups. This study did not include neurophysiological measures and the robot involved in this study only encourages movement of the wrist. Also one must note that the researchers increased the intensity by 1mA to 2mA from their previous study and the rationale behind this was not mentioned.

2.5.7 Summary of literature review

People with stroke experience problems with long-term disability which can result in a poor quality of life for survivors and their families. Although there is some provision of conventional therapy for the impaired UL only 5-20% of survivors regain full functional use of their arm and hand. Current evidence shows that neuroplasticity and motor recovery and the driving factors for this are intensity, repetition, task specificity and carried out as soon as possible after the stroke. RT can provide these driving factors and can improve UL motor impairments. NIBS such as tDCS can enhance cortical excitability and thus recovery. Therefore, recent research has focussed on the addition of tDCS to stroke rehabilitation programmes to promote UL recovery. However, inconsistent results have been reported regarding the benefit of adding tDCS to motor training such as RT in stroke. This could be due to inconsistent methodologies and robots only focusing on bilateral and distal UL movements. Therefore, carrying out a research study involving tDCS with three-dimensional and uni-lateral RT for people with stroke with UL impairments could lead to different results. In addition to UL impairments and function of people with an affected UL in stroke, measuring stroke impact and neurophysiological effects using TMS of both techniques could also lead to interesting results. Finally, none of the previous research explored the feasibility and the views and experiences of the combination NIBS and RT by people with stroke. Therefore, we proposed that using a mixed-method approach for a pilot double-blinded RCT (with a feasibility component) involving people with stroke will add to current knowledge of the combination of tDCS with stroke UL rehabilitation.

2.6 Research questions of the proposed research

There is an increased research interest and also some evidence from the clinical trials for both tDCS and RT to improve UL impairments in stroke. However, it is too early for both interventions cannot be translated into clinical practice. Anodal tDCS can increase cortical excitability and therefore potential for neuroplasticity. RT ‘drives’ the neuroplastic changes towards recovery of normal movement patterns and improved function. The theoretical rationale for combining the modalities is evident. Therefore, main research questions for this project were:

a) What is the effectiveness of multiple sessions of tDCS and rehabilitation on UL recovery following stroke?’

b) What is the feasibility of combining RT and anodal tDCS for the impaired UL in sub-acute and chronic stroke?

c) What is the effect of combining RT and anodal tDCS for impaired UL in sub-acute and chronic stroke?

To address the research questions, three separate studies were carried out. The first was a systematic review with meta-analyses exploring the combination of multiple sessions of tDCS with rehabilitation programmes for the impaired UL in stroke and this is described and discussed in the next chapter. The second was a double-blinded pilot RCT with a feasibility component exploring the feasibility and effect of the combination of anodal tDCS with RT for the impaired UL in stroke and the rationale and choice of outcome measures that is explained in the following sections. As part of the feasibility component of the pilot RCT, a third study exploring the reliability of neurophysiological measurement (RMT and MEP amplitude using TMS) was carried out.

2.7 Rationale for the chosen study designs

For the first study, a systematic review was chosen since it can present an overview of primary studies using an explicit, transparent and reproducible method (Greenhalgh et al., 2004). It is an efficient scientific technique of integrating scientific information and evaluating decision-making. A meta-analysis then adds power to the decision making from a systematic review (Mulrow, 1994).

The purpose for the RCT was to generate the data required to design a similar RCT with a larger sample. The present RCT provided enough data in order to perform a power calculation (using FMA as the primary outcome measure) and estimate the sample size for a study comparing RT and tDCS involving people with sub-acute and chronic stroke. For a pragmatic RCT to be truly effective, qualitative information is required regarding the participants' views of the acceptability of the interventions. Therefore, a 'mixed methods design' was chosen which involved a mixture of qualitative and quantitative approaches (Creswell and Clark, 2007). The feasibility component of the RCT was important to estimate important parameters such as intensity of NIBS, willingness of participants to be randomised, willingness of clinicians to recruit participants, standard deviation of the outcome measures which were needed to estimate sample size, recruitment, follow-up rates and an adherence to the protocol (Arain et al., 2010). A pilot study is a miniature version of a large study that checks whether correct choices and procedures for a larger study were made. It also focused and analysed processes such as recruitment, randomisation, treatment, and that conduction of follow-up assessments (Arain et al., 2010).

Thus, the study design chosen to answer the research question was a pilot double-blinded RCT with a feasibility component. The feasibility part explored factors such as adverse reactions, the feasibility of the protocol, timing and resources and views and experiences of participants. If there were no changes to the protocol after assessing the feasibility component, then the participants were added to the pilot RCT. The aim for the latter was to explore the main effect of the interventions and also monitored the feasibility factors by the qualitative research.

When developing the protocol there was a lack of good quality studies specifically with the outcome measures used studying this area. Therefore the exact sample size for the RCT was not able to be calculated. When comparing this project to the similar study design by Hesse et al. (2007), it was proposed that a significant improvement in UL function using the outcome measure, FMA, would be observed in a sample of ten or more participants with cortical and sub-cortical sub-acute stroke. After problems with recruitment rate, participants with chronic stroke were also added to the final sample. The following sections provide justification for the criteria, intervention and outcome measures chosen for the pilot RCT.

After the pilot RCT was carried out, as part of the feasibility component the researchers felt that further information about intra-rater and test-retest reliability of RMT and MEP amplitudes of the upper arm (deltoid) and forearm (extensor digitorum) muscles was needed.

2.8 Selection criteria and intervention for randomised controlled trial

Participants in the sub-acute and chronic stage were included in the study. The following two sub-sections will discuss the rationale and changes in the inclusion and exclusion criteria.

2.8.1 Inclusion and exclusion criteria

At first, participants needed to have a confirmed clinical diagnosis of stroke by a neurologist or stroke specialist within the two-sixteen weeks post-stroke which was defined as the sub-acute phase (Teismann et al., 2011). Following problems with recruitment in the first year of the study, chronic stroke (>16 weeks post-stroke) participants were also recruited.

The participants needed to have only a single stroke in order to eliminate any confounding factors and to be between the ages of 18 to 80 years. The rationale for the latter was that a MEP is difficult to be elicited in people above 80 years old (Talelli et al., 2008). However, once again due to the slow recruitment rate and limited evidence for the latter, the upper age limit was removed and ethical approval was also sought for this amendment (Appendix C.2). From the stroke population, 23-25% people might have a previous stroke (Kammersgaard et al., 2004), 50% might have cognitive problems (Bour et al., 2010), 3% might have epilepsy (Camilo and Goldstein, 2004) and 1% might have had brain surgery or metal implants (Solomon et al., 1996). Thus, these factors could influence the recruitment rate hence, ethical approval was obtained for the amendments and further detail can be found in Section 4.4.

To use the Armeo®Spring robot, participants needed to have good sitting balance and 45º shoulder flexion of their affected arm and also lack of shoulder pain between 90º to 180º. Additionally, they needed to have an UL hemiparesis with an overall score of 2 or above on the Medical Research Council scale for muscle strength and with minimal spasticity allowed (Modified Ashworth scale <or= 2). Finally, for ethical reasons participants needed to provide written informed consent.

Participants were excluded if they had impaired gross cognitive function; score of less than 24 on the Mini-Mental State Examination (MMSE) (Folstein et al. 1975). This was for participants to understand the procedure and the games involved in the RT and also give full informed consent. To eliminate any confounding factors, participants were excluded if they had any additional neurological conditional to the stroke. Participants were excluded from NIBS, if they had a history of epilepsy since there is a low risk of single pulse TMS and tDCS of inducing an epileptic seizure (Rossi et al., 2009). In addition if participants had metal implants, previous brain neurosurgery or pregnant were also excluded from the study. Participants that were taking selective serotonin receptive inhibitors were excluded from the TMS assessment due to these medications are prone to inducing an epileptic fit (Montgomery, 2005).

2.8.2 Intervention programme and equipment

An intervention programme involving 18 sessions of RT in addition with tDCS was chosen. Each session lasted for an hour. This session involved 20 minutes of anodal tDCS at an intensity of one mA. Anodal stimulation was chosen in order for comparison of the findings from the present study with those from the largest RCT to date involving RT and anodal stimulation (Hesse et al. 2011). Anodal tDCS was chosen to be applied during RT since there is evidence that if anodal stimulation is carried out during motor learning it can lead to faster learning than if applied prior to motor learning (Stagg et al., 2011). An intensity of 1mA was chosen since it is an appropriate parameter suggested for double-blind sham-controlled clinical studies in brain stimulation by Gandiga et al. (2006) and also to minimise any adverse reactions. In addition, the largest trial to date (n=127) involving RT consisted of one hour 32 sessions over 12 weeks (Lo et al., 2010). Therefore, a similar programme was included in the trial, however, due to the study time constraints, nine sessions of an hour each over a shorter time (six to eight weeks) were included to maintain the required intensity. The equipment chosen for the intervention were the Armeo®Spring robot and the HDCkit equipment.

2.8.2.1 Armeo®Spring robot

The Armeo®Spring arm robot is a commercially available device which facilitates intensive task-oriented arm rehabilitation developed by a company in

Switzerland called Hocoma®. The robot is an ergonomic arm exoskeleton with integrated springs and provides support for the arm against gravity (Hocoma, 2012). This enables people with stroke with UL impairments to achieve an increased range of movement. The Armeo®Spring allows variable levels of support against gravity and also provides a large three Dimensional (3D) workspace including sensors of arm movement and hand grip. This allows users to interact with therapeutic computer games and receive feedback about performance (Housman et al., 2009).

2.8.2.2 HDCkit (tDCS stimulator)

The HDCkit® is a tDCS stimulator developed by an Italian company called Newronika® (Newronika, 2012). This equipment has 'real' and 'sham' stimulation settings and allows an intensity of 0.5mA to 1.5mA. In the sham option, the direct current is switched off after 10 seconds, thus the participant feels the initial sensation but does not receive further stimulation. Sham tDCS conditions are indistinguishable from anodal tDCS conditions (Gandiga et al., 2006).

2.9 Clinical measures selected for the randomised controlled trial

Six clinical measures were selected to assess UL impairments and function, activities and participation in this stroke research. These measures were chosen because they assessed the global recovery of UL impairments, function and dexterity, ADLs, stroke impact and depression and anxiety. In addition neurophysiological measures, using TMS, were used to measure changes in cortical excitability.

2.9.1 Primary outcome measures

The primary outcome measures chosen for the research were the Fugl-Meyer Assessment (FMA) and cortical excitability (Appendix E.4.1).

2.9.1.1 Fugl-meyer assessment

The FMA, is a quantitative measure using methods by Brunnstrom assessing motor recovery, sensation, joint range of motion and co-ordination of the impaired upper and lower limbs of people with stroke (Fugl-Meyer et al., 1975).

The test was developed using the theory that recovery of motor function follows an obligatory sequence. It is one of the most widely used quantitative measures of motor impairment (Gladstone et al., 2002). According to the International Classification of functioning, disability and health (ICF), FMA assesses body impairments and the maximum motor score for the upper extremity section is 66 (Duncan et al., 1983).

The minimal detectable change of the FMA was found to be 5.2 points in people with chronic stroke (van der Lee et al., 2001). However, it was reported that a Minimally Clinically Important Difference (MCID) from admission to discharge of people with acute stroke was 10 points of FMA UL section (de NAP Shelton and Reding, 2001, Page et al., 2012). It was also reported that the UL motor score FMA has excellent test-retest reliability (ICC = 0.97) (Platz et al., 2005a) and excellent inter-and intra-rater reliability (*r* =0.995 - 0.996) in acute and chronic stroke (Duncan et al., 1983, Platz et al., 2005a, Sullivan et al., 2011). Additionally, the measure has been found to have excellent internal consistency in acute and sub-acute stroke when assessed 14, 30, 90 and 180 days after stroke (alpha = 0.94 to 0.98) across four administrations (Lin et al., 2004). FMA has also been shown to have very good to excellent criterion and construct validity in acute stroke (r=0.86-0.96) and moderate to excellent construct validity in chronic stroke (Malouin et al., 1994, Hsieh et al., 2009).

Therefore, the motor section of the measure has been demonstrated to have excellent validity and reliability. Limitations include that it only measures gross motor movements and does not measure function and distal fine movements. Therefore, it was decided that this measure is not enough to measure hand movement and an additional measure called the Action Research Arm Test (ARAT) was used which is discussed in section 2.9.2.1.

2.9.1.2 Measurement of cortical excitability

Motor Evoked Potentials (MEPs) can be evoked by using TMS and EMG in stroke. In order to evoke MEPs from the affected hemisphere controlling the impaired UL after a stroke, a figure of eight magnetic coil needs to be placed on that affected hemisphere. The size of the MEPs can be considered as a measure of changes in cortical excitability of the M1. The optimal spot called the 'hotspot' for evoking MEPs from the arm and hand muscles is recorded and the resting motor threshold (RMT) is the optimal intensity needed to evoke a MEP from the muscles at rest. The RMT can be defined as the minimal stimulus intensity that evokes five MEPs out of 10 with amplitude of 50 µV (Rossini and Rossi, 1998). This kind of assessment is often used in stroke research, however evidence of the psychometric properties of this technique is limited. The reliability of this measurement showed good to excellent reliability (ICC=0.60-0.92) when measuring MEP thresholds, however, low reliability for MEP amplitude of hand muscles in young adults (ICC = 0.01 to 0.34) (Livingston and Ingersoll, 2008). Good to high reliability of measurement of MEP amplitude of the abductor digiti minimi muscles was found in older adults (Christie et al., 2007). Only one study explored the variability of MEP measurement at the hand extensor muscles in chronic stroke and they found large fluctuations in MEP amplitude between sessions (Andrew et al., 2005). No studies were found exploring the validity of the measurement. These mixed results led to the development of neuronavigation techniques such as the Brainsight® when using TMS to improve the reliability of the measurement. Various studies have used this equipment for this procedure (Lotze et al., 2009, Rushworth et al., 2001). More information how this equipment was used in our study can be found in Chapter four.In this study MEP of the anterior deltoid and extensor digitorum communis muscles were measured. These muscles were chosen since the anterior deltoid is the main proximal muscle used during RT (Gijbels et al., 2011) and the distal wrist extensor muscle was used are intensively used when releasing the grip during the RT using the Armeo®Spring.

2.9.2 Secondary outcome measures

The secondary outcome measures chosen were the Action Research Arm Test (ARAT), Modified Tardieu Scale (MTS), Motor Activity Log-28 (MAL), Stroke Impact Scale 3.0 (SIS) and Hospital Anxiety and Depression Scale (HAD) (Appendix E.4.1).

2.9.2.1 Action research arm test

The ARAT measure consists of a wooden shelf, which is placed on a table in front of the participant with UL impairments (Lyle, 1981). This measure is split up into three subtests (grasp, grip, pinch), involving testing the ability to grasp, move, and release objects differing in size, weight, and shape. The maximum score that can be obtained is 57. A change of 10% or six points out of 57 has been shown to be a clinical importance difference (van der Lee et al., 2001). ARAT has excellent intra- and inter-rater reliability with people with chronic stroke (Spearman's rho and ICC=>0.98) and excellent good construct validity (Spearman's rho: 0.925) was found in people with sub-acute and chronic stroke with arm hemiparesis (van der Lee et al., 2001, Platz et al., 2005a). The advantage of the ARAT measure is that in the acute phase when UL function is limited, it provides the assessor to stop testing. However, some of the tests can be difficult for people with stroke and therefore, floor effects can be demonstrated (Platz et al., 2005a). In addition, if a person has shoulder pain it can limit lifting objects onto the shelf.

2.9.2.2 Modified tardieu scale

The Modified Tardieu Scale (MTS) is a measurement of impairment and quantifies muscle tone by measuring the intensity of muscle reaction at a specified velocity. This measure was chosen in order to ensure that spasticity and biomechanical stiffness does change after the RT and NIBS intervention in the proposed research. The assessor does not only take into consideration the amount of resistance at a specific velocity but also at what angle a muscle reaction occurs. This measure involves measuring the quality of muscle reaction and the angle of catch during fast velocity of the limb.

Literature tends to favour Tardieu Scale in paediatrics rather than with adults with neurological conditions (Boyd et al., 1999). In a cross-sectional analytical study by compared the level of agreement of the Ashworth Scale (another measure of spasticity) and the Tardieu Scale with laboratory measures in detecting spasticity and contracture at the elbow joint of people with stroke (Patrick and Ada, 2006). They demonstrated a percentage exact agreement of 63% between the Ashworth Scale and the laboratory measure. However, a 100% agreement between the Tardieu Scale and the laboratory measure in the presence of spasticity and a 94% agreement in the presence of contracture. Therefore, they concluded that the Tardieu Scale is a more reliable measure of spasticity than the Ashworth Scale, however, it takes longer to be administered in clinical practice. The same researchers found Tardieu Scale having good validity (a significant and moderate correlation r=0.62) as a measure of spasticity at the elbow joint of 16 patients three years post-stroke. However, one must note that since Tardieu Scale is an ordinal tool, Pearson's correlation could have been inappropriately utilised since it is usually used with interval/ratio data.

Boyd et al. (1999) further modified the Tardieu Scale as the Modified Tardieu Scale (MTS) which specifies at which position the muscle needs to be tested. MTS was found to have moderate to excellent test-retest reliability (k = 0.52-0.87) in people with brain injury (Mehrholz et al., 2005). However, if the raters are in-experienced, moderate reliability was found in people with elbow spasticity after stroke (Ansari et al., 2008). In the present study, the MTS was utilised for measurement of spasticity at the elbow flexors and wrist extensors (anti-gravity muscles) since spasticity develops in the anti-gravity muscles in people with and also these two muscles are used intensively during RT intervention (Welmer et al., 2010).

2.9.2.3 Motor activity log-28

The MAL was used to register the use of the paretic hand in daily activities by the participants. This measure assesses activity limitation due to impairments in the UL. The MAL is a semi-structured interview during which respondent's rate how well [quality of movement scale (QOM)] and how much [amount of use scale (AOU)] they use their impaired arm during 30 UL activities of daily living. The summary score is the mean of the item scores (Hammer and Lindmark, 2010, Uswatte et al., 2006). In people with stroke, the measure has been shown to be responsive to change and also demonstrated medium construct validity (Hammer and Lindmark, 2010). An item analyses was performed, and removal of two items from the measure was carried out (Uswatte et al., 2006). Therefore, the measure was changed to a 28-item tool. The researchers demonstrated that the QOM section was reliable (r=0.82) and validity was also supported. Due to time constraints, the quality of movement (QOL) section of this measure was selected for the present study. Research have demonstrated that the amount of UL use and the QOL sections are very similar and highly correlated (Uswatte et al., 2006).

2.9.2.4 Stroke impact scale

The SIS evaluates function and quality of life in eight clinically relevant domains on the basis of self-report, thus measures participation of the ICF model. The second version was demonstrated as valid and reliable (Duncan et al. 1999). SIS 2.0 was shown to be responsive to change from the first to the third and sixth month post-stroke however, not responsive between the third and sixth months for people with mild and moderate strokes for the domains of hand function, mobility, ADLs, combined physical, and participation(Duncan et al., 1999). Rasch analysis carried out by Duncan et al. (2003) led to some deleted items and resulted in the version 3.0 of the SIS. The hand function domain of the measure has been showed moderate responsiveness and criterion validity in people with chronic stroke (Lin et al., 2010).

2.9.2.5 Hospital depression and anxiety Scale

HAD was developed to identify depression and anxiety disorders experienced by patients in non-psychiatric hospital clinics (Zigmond and Snaith, 1983). HAD has shown to have high sensitivity and internal consistency, however, low specificity in people with post-stroke (Johnston et al., 2000, Johnson et al., 1995).

In addition Armeo® assessments were also carried out during every intervention session. These assessments have shown moderate to excellent reliability (Rudhe et al., 2012). More detail about these assessments is found in Chapter four.

2.9.3 Screening assessments

The main measures chosen for the screening procedure were the MAS, Medical Research Council Strength Test and the Mini-Mental State Examination.

The MAS is a single-item measure and describes the resistance perceived while moving a joint through its full range. Reflex activity at the lower end of the scale is classified by a phenomenon called a ‘catch’ (Bohannon and Smith, 1987). Studies have shown that it has moderate to very good intra-, inter- and test-retest reliability in brain injury but poor reliability at the elbow in people with hemiplegia (Mehrholz et al., 2005, Ansari et al., 2008). However, the latter study involved clinicians using the MAS without any experience. Poor validity has been demonstrated of this measure when used at the UL in stroke (Patrick and Ada, 2006).

The MRC strength test is a manual muscle test which uses numeral grades from zero to five (Medical Research Council, 1976). The chosen muscles to be screened in this research study were of the shoulder, elbow, wrist and hand of the affected UL in order to get a general overview of the strength of the UL for RT. Studies have shown substantial reliability and validity of measurement of the wrist muscles in radial palsy (Paternostro-Sluga et al., 2008). In addition, 16 muscles were tested for reliability in Duchenne's muscular dystrophy which showed moderate to excellent reliability (k=0.65-0.93) with the proximal muscles having higher reliability (Florence et al., 1992). However, these studies did not measure the psychometric properties involving people with stroke. Therefore, properties must be interpreted with caution.

MMSE is a screening tool for level of cognitive function and detecting cognitive impairment (Folstein et al., 1983, Dick et al., 1984). It has been used as an initial assessment of cognitive function of people with stroke however with moderate validity (Zwecker et al., 2002). This measure was required as a screening tool for our study in order for the participants to provide informed consent and also understand the RT procedure.

2.10 Conclusion

This chapter presented a literature review about stroke and problems that survivors encounter such as UL impairments, reduced activities and participation. A general overview about neuroplasticity and motor learning was then presented in relation to the rehabilitation programmes such as RT and NIBS applications provided for the UL in stroke. From the review it was concluded that three studies were required. The first was a systematic review with meta-analyses questioning the evidence of multiple sessions of tDCS and rehabilitation programmes for the UL in stroke that is discussed in the following chapter. The second was a double-blinded pilot RCT exploring the effect of tDCS and three-dimensional uni-lateral RT for the impaired UL in stroke which will be presented in chapter four and the final study explored the reliability of the neurophysiological measurement of cortical excitability which will be presented in Chapter five.

Chapter 3

Systematic Review and Meta-Analyses

3.1 Introduction

Upper limb (UL) impairments are common in stroke. Non-invasive Brain Stimulation (NIBS) techniques, such as transcranial Direct Current Stimulation (tDCS), involve applying stimulation to the motor cortex with the aim of reducing UL impairments (Hummel et al., 2005, Bolognini et al., 2011, Hesse et al., 2011).

Recent systematic review and meta-analyses have explored the effect of tDCS on UL activity in stroke (Bastani and Jaberzadeh, 2011, Adeyemo et al., 2012, Butler et al., 2013, Elsner et al., 2013). Adeyemo et al. (2012) conducted a review exploring the effects of repetitive Transcranial Magnetic Stimulation (rTMS) and tDCS on outcome and discussed the parameters of stimulation and clinical trial design. A significant pooled effect size (0.58) of both rTMS and tDCS on motor function was found. Bastani and Jaberzadeh (2011) explored the effect of anodal tDCS on UL movements in healthy controls and people with stroke. They reported that anodal tDCS had a small non-significant effect size (0.39) on hand function in stroke, but a moderate significant effect size (0.59) on Motor Evoked Potential (MEP) amplitude. Butler et al. (2013) also explored the effect of anodal tDCS on UL motor recovery and also demonstrated a significant effect size of (0.40).

A recent Cochrane review showed that tDCS has a small effect on motor impairments post-intervention but not on Activities of Daily Living (ADLs) (Elsner et al., 2013). However, at follow-up they showed an effect of tDCS on ADLs but not on UL motor impairments. No effect of tDCS in sub-groups involving people with acute, sub-acute and chronic stroke was reported.

It is essential to understand in detail and question the effectiveness of combining tDCS and rehabilitation interventions for UL motor recovery in stroke. The majority of the studies included in the reviews were mainly studies including only one session of tDCS. Therefore, the evidence for effectiveness of multiple sessions of tDCS combined with rehabilitation for the recovery of UL function in stroke is currently equivocal and also limited. A potential reason for this could be due to the different methodologies used when applying tDCS. These include variation in the intervention protocol and trial design such as the outcomes used and different tDCS parameters. Therefore, a systematic review with meta-analyses exploring the effect of multiple sessions tDCS and rehabilitation techniques on UL motor function in stroke was conducted for this Doctor of Philosophy degree.

3.2 Research question and objectives

The research question for the review was: 'What is the effectiveness of multiple sessions of tDCS and rehabilitation on UL recovery following stroke?'

The objectives of the review were:

- To review and explore the effect of multiple sessions of anodal, cathodal and bihemispheric tDCS combined with rehabilitation on UL impairments in stroke
- To review and explore the effect of multiple sessions of anodal, cathodal and bihemispheric tDCS on UL dexterity in stroke
- To review and explore the effect of multiple sessions of anodal, cathodal and bihemispheric tDCS on UL ADLs in stroke
- To review and explore the effect of multiple sessions of anodal, cathodal and bihemispheric tDCS on cortical excitability in stroke

3.3 Eligibility criteria

The criteria for this review for the type of studies, participants, interventions, adverse reactions, type of outcomes and search methods for identification of studies are described in the following sub-sections.

3.3.1 Type of studies

- Randomised Controlled Trials (RCTs) that utilised either a sham control and/or another comparative therapy group
- Cross-over studies
- Both blinded and un-blinded studies

3.3.2 Participants

Studies with the following participant inclusion criteria were included in this review:

a) Have a confirmed clinical diagnosis of a haemorrhagic or an ischaemic stroke using the World Health Organisation definition:

"a syndrome of rapidly developing symptoms and signs of focal, and at times, global, loss of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin" (Aho et al., 1980: 114)

b) Experienced a single or multiple strokes

c) In the acute (starting intervention during the first 2-weeks post-stroke), sub-acute (starting intervention at 2 weeks to four months post-stroke) or chronic (starting intervention after four months post-stroke) phases of stroke recovery

d) Any type and location of stroke

e) Male or female over the age of 18 years

f) With any type of UL impairment.

3.3.3 Interventions and specific comparisons

Trials including tDCS combined with other interventions were included in this review. Interventions utilising tDCS for therapeutic use were chosen. Different stimulation parameters were included (dosage/intensity, mode of delivery, frequency, duration and timing of delivery). Invasive brain stimulation studies were excluded. Interventions were compared with an active controlled intervention including sham stimulation in addition with different types of therapy such as physiotherapy or robot therapy (RT).

3.3.4 Type of outcomes

The primary outcome measures chosen were clinical measures of UL motor impairment such as FMA (UL Section) (Fugl-Meyer et al., 1975) and neurophysiological (Rossini and Rossi, 1998). Various secondary UL outcome measures were considered such as UL dexterity measures, activities of daily living and stroke impact measured at baseline, during, post-intervention and at follow-up.

3.3.5 Adverse effects

These were also recorded if reported in the studies

3.3.6 Search methods for identification of studies

A computerized search was carried out for full papers and abstracts published and reported in English published between 1990 and September 2013. The electronic databases MEDLINE, EMBASE (Excerpta Medica Database), Cochrane Library (Cochrane Controlled Trials Register) and CINAHL (Cumulated Index of Nursing and Allied Health Literature), PubMed and Physiotherapy Evidence Database (PEDRO) were systematically searched by the main researcher (LTT). Key words and combinations of key words were used for the search on the electronic databases. Different combinations of the topics were inputted with the use of 'AND' and 'OR' to achieve a specific selection of literature.

The key words chosen were the following: 'transcranial direct current stimulation', 'stroke/ or exp brain stem infarctions/ or exp cerebral infarction/', 'cerebrovascular accident', 'exp Motor Activity/' 'Recovery of Function'; 'upper extremity/ or exp arm/ or exp axilla/ or exp elbow/ or exp forearm/ upper extremity/ or exp shoulder/', 'upper extremity/ or exp fingers/ or exp metacarpus/ or exp wrist', 'hemiparesis', 'hemiplegia'**.**

3.4 Data collection and qualitative analysis

The selection of the studies, data extraction and management and data analysis for the review and meta-analyses are discussed in the following sub-sections.

3.4.1 Selection of studies

The reference lists of each database containing the articles and narrative reviews were scanned separately for relevant publications and selected based on title and abstract by LTT. Any conference abstracts were excluded. After reading the full texts, the studies were categorised by LTT according to the following: irrelevant, possibly relevant, and relevant. Studies were excluded when there was clear indication from the title or abstract that the study was not relevant or did not meet the selection criteria. If it was unclear, then two researchers (Dr Ann-Marie Hughes [AMH] or Dr Geert Verheyden [GV]) assessed the full paper and a joint decision was made. The included papers were divided in two groups. All papers were reviewed by LTT and 50% of the papers were reviewed by AMH and the remaining 50% were reviewed by GV.

Disagreement between reviewers was resolved through discussion between the two review authors. Where resolution was not achieved a fourth reviewer (Professor Jane Burridge [JHB]) considered the paper(s) in question. Agreement was reached in all cases.

3.4.2 Data extraction and management

Three review authors (LTT, AMH and GV) extracted data independently using a standardised valid and reliable form called the modified Downs and Black form. This checklist was developed by Downs and Black (1998) and later modified by Eng et al. (2007) which assesses the methodological quality both of randomised and non-randomised studies of health care interventions (Appendix A).

The form contains 27 ‘yes’-or-'no’ questions across five sections. The tool is easy to use and provides both an overall score for study quality and a numeric score out of a possible 30 points. The five sections include questions about: 1) study quality (10 items) – the overall quality of the study; 2) external validity (3 items) – the ability to generalise findings of the study; 3) study bias (7 items) – to assess bias in the intervention and outcome measure(s); 4) confounding and selection bias (6 items) – to determine bias from sampling or group assignment and 5) power of the study (1 item) – to determine if findings were due to chance.

3.4.3 Data analysis

The hypothesis, sample size, type of study, participants, intervention, outcome measures and conclusions were recorded for each selected paper. Data from the Modified Downs and Black form were pooled and divided into study quality, external validity, study bias and confounding bias and power of the study.

Each paper was then analysed for possible meta-analyses. The Cochrane Collaboration's Review Manager software, RevMan (Version 5.1), was used for all analyses (CochraneCollaboration, 2011). All outcome measures were analysed as continuous data. Authors were contacted to obtain unreported data for the selected studies. The mean, standard deviation and number of participants at post-intervention for the real and sham groups were inputted to the program. The standardised mean differences (SMD) (using Hedges’ adjusted g) and 95% confidence intervals were calculated. Hedges' adjusted (g), which is similar to Cohen's (d) tested the effect size but it also includes an adjustment for small sample bias of RCTs. The effect size was interpreted with Cohen's convention of small (0.2), medium (0.5), and large (0.8) effects (Cohen, 1988). A fixed-effect model was applied when the studies involved similar populations, interventions, same outcome measure and had heterogeneity (*I*) of less than 50%. This model assumes one true effect size which means that all differences of the observed effects are due to sampling error. In addition, the random-effects model was used when heterogeneity (*I*) was more than 50% (Borenstein et al., 2011). It was also applied which considers that the true effect varies from one study to the other due to different interventions and different populations.

3.5 Results - Qualitative analysis

Nine papers were excluded due to irrelevant methodology from the 13 abstracts initially found. Therefore, four papers were qualitatively analysed by the three reviewers. From two additional searches carried out in October 2012 and September 2013, four additional papers were included. Thus, a total of eight papers were reviewed (Figure 3.1).

A total score of 15 and above on the Modified Down and Black form was considered as a high quality score (Cappuccio et al., 2011). Seven papers scored 16 points and above demonstrating high quality methodology (Eng et al., 2007) (Table 3.1). The study by Ochi et al. (2013) scored a score of 13 points, demonstrating low quality and therefore was not included in the analyses. More detail about the scores of each paper can be found in the Appendix A.1. The rated scores for methodology quality for each included paper are presented in Table 3.1.

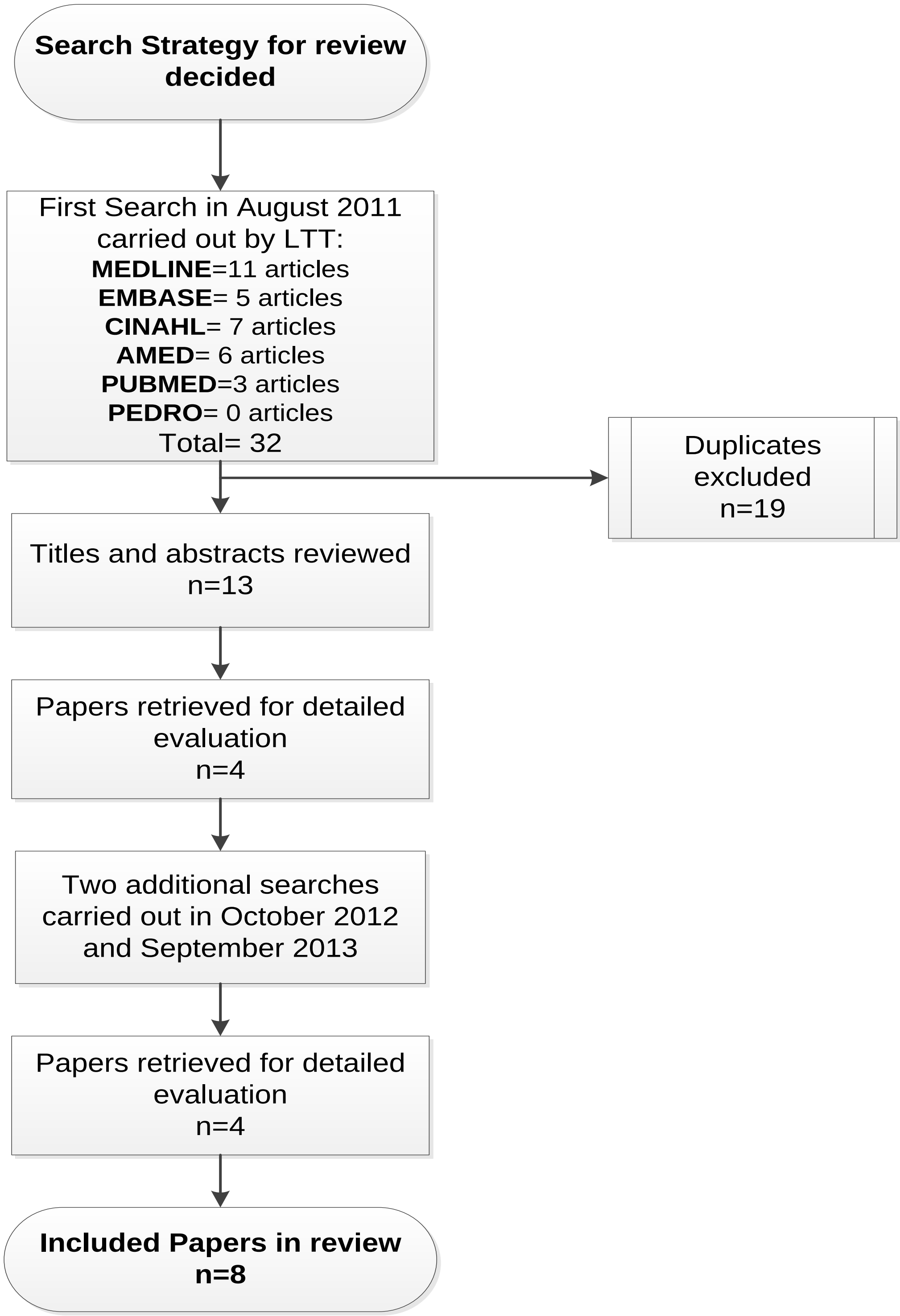

Figure 3.1 Prisma flow diagram: selection process of papers for the review

3.5.1 Included studies

The detail of the included studies is demonstrated in Table 3.3.

Table 3.1 Methodological Quality of the Reviewed Papers

Study/ Downs and Black Domain	Kim et al., 2010	Lindenberg et al., 2010	Bolognini et al., 2011	Hesse et al., 2011	Nair et al., 2011	Khedr et al., 2013	Ochi et al., 2013	Wu et al., 2013
Reporting (score out of 11)	9	8	9	11	8	9	9	9
External validity (score out of 3)	2	1	0	0	0	3	0	2
Internal validity (bias) (score out of 7)	6	6	6	6	6	7	4	5
Confounding bias (score out of 6)	4	2	1	4	3	4	0	7
Power of study (score out 1)	0	1	0	1	0	0	0	0
Total Score (out of 28)	**21**	**18**	**16**	**22**	**17**	**24**	**13**	**23**

3.5.2 Study design

The selected studies were of RCT design (Kim et al., 2010, Lindenberg et al., 2010, Bolognini et al., 2011, Hesse et al., 2011, Nair et al., 2011, Khedr et al., 2013, Wu et al., 2013). All the studies had sham and real groups. One study was single-blinded (Kim et al., 2010) and the other six were double-blinded (Lindenberg et al., 2010, Bolognini et al., 2011, Hesse et al., 2011, Nair et al., 2011, Khedr et al., 2013, Wu et al., 2013). The sample sizes of the studies ranged from 14 to 96 people with stroke. Two studies had a sample size over 50 (Hesse et al., 2011, Wu et al., 2013); the remainder had smaller samples ranging from 14 to 40 (Lindenberg et al., 2010, Kim et al., 2010, Bolognini et al., 2011, Nair et al., 2011, Khedr et al., 2013).

3.5.3 Population characteristics

In total, 292 participants with stroke (196 males) were included in the review. Four studies did not report the handedness of the participants (Kim et al., 2010, Hesse et al., 2011, Khedr et al., 2013, Wu et al., 2013). The other studies reported that 48 participants were right-handed and one was ambi-dextrous. All participants had a single stroke. Limited detail was provided about the stroke location. In general, 133 (46%) participants had cortico-subcortical or cortical strokes and 49 (17%) participants had subcortical stroke. Two studies did not describe the location of the strokes (Lindenberg et al., 2010, Wu et al., 2012). Three studies involved 45 (16%) participants with chronic stroke (Lindenberg et al., 2010, Bolognini et al., 2011, Nair et al. 2011), three studies involved 204 (70%) participants in the sub-acute stage (Kim et al., 2010, Hesse et al., 2011, Wu et al., 2013) and one study involved 40 (14%) people with acute stroke (Khedr et al. 2013). More information about the population is presented in Table 3.2.

Table 3.2 Characteristics of the participants selected for the studies

Characteristic	% Population (n=292)
Stage of Stroke	16% Chronic 70% Sub-Acute 14% Acute Stroke
Type of Stroke	17% Haemorrhagic 77% Ischaemic 6% Unknown
Upper Limb Impairments*	0.01% Mild 23% Moderate 64% Severe

* Based on the FMA measure: 0 to 20 have severe UL impairments, 21 to 50 have moderate UL impairments and 51 to 66 have mild impairments (Velozo and Woodbury, 2011, Fugl-Meyer et al., 1975)

UL severity was classified as ‘severe’, ‘moderate’ and ‘mild’ by the first researcher (LTT) based on the classification on the FMA (Velozo and Woodbury, 2011). Four (0.01%) participants had mild UL impairments based on the FMA outcome measure (Lindenberg et al., 2010), 66 (23%) participants had moderate UL impairments (Kim et al., 2010, Bolognini et al., 2011, Ochi et al., 2013, Khedr et al., 2013, Lindenberg et al., 2010, Nair et al., 2011) and 186

(64%) participants had severe UL impairments (Hesse et al., 2011, Wu et al., 2013). The study by Khedr et al. did not measure UL motor impairments using FMA and therefore the UL global impairments of the sample were unknown.

3.5.4 Country

The studies were conducted in a number of countries and therefore represent different healthcare systems. In Europe, studies were based in Germany (Hesse et al., 2011) and Italy (Bolognini et al., 2011). Two studies were based in the USA (Lindenberg et al., 2010, Nair et al., 2011). In Asia, one study was based in Korea (Kim et al., 2010), another in China (Wu et al., 2012). The final study was based in Egypt (Khedr et al., 2013).

3.5.5 Outcome measures and timing of assessments

The FMA was used as an outcome measure of UL motor impairments by six studies (Kim et al., 2010, Lindenberg et al., 2010, Bolognini et al., 2011, Hesse et al., 2011, Nair et al., 2011, Wu et al., 2013), and one study used the MRC scale as an outcome motor measure (Khedr et al., 2013). Two studies explored the neurophysiological effects of tDCS, such as the Resting and Active Motor Threshold (Bolognini et al., 2011, Khedr et al., 2013) and transcallosal inhibition (Bolognini et al., 2011). The Modified Ashworth Scale was the main outcome measure used to measure spasticity (Hesse et al., 2011, Wu et al., 2013).

Block test (Hesse et al., 2011), Jebsen Taylor Hand Function Test (Bolognini et al., 2011) and Wolf Motor Function Test (Lindenberg et al., 2010) were used as measures of UL dexterity. The Barthel Index or Modified Barthel Index and Motor Activity Log were utilised as measures of activities of daily living (Kim et al., 2010, Hesse et al., 2011, Khedr et al., 2013, Wu et al., 2012). Two studies also involved functional MRI as an outcome measure of brain activity (Lindenberg et al., 2010, Nair et al., 2011).

Table 3.3 Characteristics of studies included in the review

Study	Objectives (To investigate:)	Design	N	Mean Age (years)	Time since stroke	Groups	tDCS Stimulation Intensity/ Duration/ Hemisphere	Training Period (weeks)	Outcomes
Kim et al., (2010)	tDCS and OT on UL motor recovery	Single-blind, sham-controlled randomised study	18	53.6-82.9	2.0 months	Anodal/ cathodal/ sham tDCS	• 2 mA • 20 mins • Ipsi-lesional hemisphere • tDCS during rehabilitation	10 sessions over 2 weeks and 30 mins OT	FMA* MBI*
Lindenberg et al., (2010)	tDCS and PT and OT on UL motor recovery	Double blinded sham-controlled randomised study	20	55.8	40.3 months	Bi-hemispheral/ sham tDCS	• 1.5 mA • 30 mins • tDCS during rehabilitation • Anode (ipsi-lesional) cathode contra-lesional	5 daily sessions of 60 mins OT and PT	FMA WMFT*
Bolognini et al., (2011)	Bihemispheric tDCS and CIMT on UL motor recovery	Double-blinded sham controlled randomised trial	14	30-75	7-105 months	Bi-hemispheric/sham groups	• 2mA • 40 mins • tDCS during rehabilitation • Anode (ipsi-lesional) cathode contra-lesional	14 daily sessions of four hours CIMT	FMA, JTT*, HG*, MAL*, BI*, MEP and Trans-collosal inhibition
Hesse et al., (2011)	tDCS and RT on UL motor recovery	Double-blinded sham controlled randomised trial	96	3 groups: (1) 63.9 (2) 65.4 (3) 65.6	3.4-3.8 weeks	Anodal/ cathodal/ sham groups	• 2mA • 20 mins • tDCS during rehabilitation • Anodal over ipsi-lesional, cathodal over contra-lesional	30 sessions over 6 weeks involving 20 mins RT	FMA, MRC*, MAS*, BI, BBT*

Study	Objectives *To investigate*:	Design	N	Mean Age (years)	Time since stroke	Groups	tDCS Stimulation Intensity/ Duration/ Hemisphere	Training Period (weeks)	Outcomes
Nair et al., (2011)	Cathodal/ sham tDCS + OT on UL motor recovery	Randomised double blind, sham controlled study	14	2 groups: 61;56	28-33 months	Cathodal; sham groups	• 30 mins • 1mA • tDCS during rehabilitation • Cathode over contra-lesional motor	5 daily sessions of 1 hour OT	ROM*; FMA fMRI*
Ochi et al., (2013)	tDCS and RT* on UL motor recovery	Double-blinded randomised controlled cross-over study	18	3 groups: 61.1	4.4 months	Anodal, cathodal, sham groups	• 10mins • 1mA • tDCS during rehabilitation • Anodal over ipsi-lesional, cathodal over contra-lesional M1	5 daily sessions RT (? Duration of each session	FMA,MAS*, MAL
Khedr et al., (2013)	Anodal/cathodal/sham tDCS + Rehabilitation on UL motor recovery	Pilot randomised double-blinded controlled trial	40	3 groups: 58.7, 60, 57	13.8,12.3 12.6 weeks (sub-acute)	Anodal, cathodal, sham groups	• 25 mins • 2mA • tDCS before rehabilitation • Anodal over ipsi-lesional, cathodal over contra-lesional M1	6 daily sessions of one hour rehabilitation	National Institute of Health Stroke Scale, Orgogozo Stroke Scale, MRC*
Wu et al., (2013)	Cathodal tDCS and rehabilitation on UL motor recovery and spasticity	Double-blind, sham-controlled, randomised controlled Design	90	2 groups: 15-70	2-12 months	Cathodal, sham groups	• 20 mins • 1.2mA • ? tDCS delivery • ? cathode placed on contra-lesional or ipsi-lesional M1	5 sessions per week for 4 weeks of 30 minutes (twice daily) PT	FMA, MAS, BI

*** BI=Barthel Index, BBT=Box and Block Test, fMRI=functional Magnetic Resonance Imaging, FMA=Fugl-Meyer Assessment, HG=Hand Grip, MAS=Modified Ashworth Scale, MAL=Motor Activity Log, MBI=Modified Barthel Index, MEP= Motor Evoked Potential, MRC=Medical Research Council Strength, ROM=Range of Motion, MT=Motor Threshold, OT= Occupation Therapy, PT= Physiotherapy, WMFT=Wolf Motor Function Test**

All studies had a baseline and post-intervention assessment session. Follow-up assessments varied between seven days (Lindenberg et al., 2010), two weeks (Bolognini et al., 2011), four weeks (Wu et al., 2013, Bolognini et al., 2011), three months (Hesse et al., 2011, Khedr et al., 2013) and six months (Kim et al., 2010). Three studies reported the timing of the assessments which were carried out at one day (Kim et al., 2010), three days (Lindenberg et al., 2010) and six days (Nair et al., 2011) after the intervention was finalised.

3.5.6 Intervention programmes

This section focuses on the applied tDCS parameters, the rehabilitation programmes and the side effect and adverse reactions reported in the studies.

3.5.6.1 tDCS parameters

The tDCs current intensity varied between studies from 1mA (Nair et al., 2011, Ochi et al., 2013), 1.2mA (Wu et al., 2013), 1.5mA (Lindenberg et al., 2010) to 2mA (Kim et al.,2010, Hesse et al., 2011, Hesse et al., 2011, Khedr et al., 2013). Three studies involved an anodal, cathodal and sham group (Kim et al., 2010, Hesse et al., 2011, Khedr et al., 2013, Ochi et al., 2013), two studies involved a cathodal and sham group (Nair et al., 2011, Wu et al., 2013) and two studies involved bihemispheric tDCS and sham groups (Lindenberg et al., 2010, Bolognini et al., 2011).

Stimulation time also varied from 20 minutes (Kim et al., 2010, Hesse et al., 2011, Wu et al., 2013), 25 minutes (Khedr et al., 2013), 30 minutes (Lindenberg et al., 2010, Nair et al., 2011) to 40 minutes (Bolognini et al., 2011). In addition, there was an inconsistency when the tDCS was administered. This was either during (Kim et al., 2010, Lindenberg et al., 2010, Bolognini et al., 2011, Hesse at al., 2011, Nair et al., 2011), before rehabilitation (Khedr et al., 2013) or not reported (Wu et al., 2013). The sham tDCS involved 30 seconds of stimulation (Wu et al., 2013, Bolognini et al., 2011, Lindenberg et al., 2010), two minutes (Khedr et al., 2013) or one minute of stimulation (Kim et al., 2010). Two studies did not provide information about the sham setting (Hesse et al., 2011) or the length of the sham setting (Nair et al., 2011).

Electrode size used differed between studies from 35cm^2 (Hesse et al., 2011, Bolognini et al., 2011, Khedr et al., 2013), to 25cm^2 (Kim et al., 2010, Wu et al., 2013), to 16.3cm^2 (Lindenberg et al., 2010). Location of the reference electrode was also different between studies. This was placed on the contralateral orbit (Kim et al., 2010, Hesse at al., 2011, Nair et al., 2011, Khedr et al., 2013), the unaffected shoulder (Wu et al., 2013) or the unaffected hemisphere for bihemispheric stimulation (Bolognini et al., 2011, Lindenberg et al., 2010).

3.5.6.2 Rehabilitation programmes

These were also different between studies. One study included the rehabilitation programme called Constraint Induced Movement Therapy daily for 14 days (Bolognini et al., 2011). Three studies included conventional therapy for 30 minutes, 5 days per week, for four weeks (Wu et al., 2013) or daily for five weeks (Lindenberg et al., 2010, Nair et al., 2011) or six days (Khedr et al., 2013). Studies included an occupational therapy programme for 10 sessions over 2 weeks (Kim et al., 2010) or bilateral wrist robot therapy for 20 minutes for 30 sessions (weekdays) (Hesse et al., 2011).

3.5.6.3 Sensations and adverse reactions

Five studies reported sensations and adverse reactions from tDCS. Participants reported tingling or slight itching under tDCS electrodes (Wu et al., 2013, Hesse et al., 2011, Lindenberg et al., 2010). One participant discontinued anodal tDCS because of a headache and one participant receiving cathodal tDCS reported dizziness (Kim et al., 2010, Hesse et al., 2011).

3.6 Results - Quantitative analysis

Seven meta-analyses were carried out based on the International Classification of Functioning, Disability and health framework- impairments and activities (WHO, 2001). Therefore, the analyses were separated on the effect of tDCS and rehabilitation on impairment and activity. Only one study included a participation measure (Khedr et al., 2013) and therefore could not be analysed by meta-analysis.

3.6.1 The effect of real versus sham tDCS and rehabilitation on upper limb motor impairments

The first meta-analysis involving five studies explored the effect of real versus sham tDCS combined with rehabilitation programmes on UL motor impairments measured by FMA. The data of the anodal and sham groups was inputted from studies involving three groups of anodal/cathodal/sham tDCS stimulation (Kim et al., 2010, Hesse et al., 2011).

An overall small non-significant effect size of +0.02 favoured real tDCS and rehabilitation compared to sham stimulation at post-intervention (Figure 3.2).

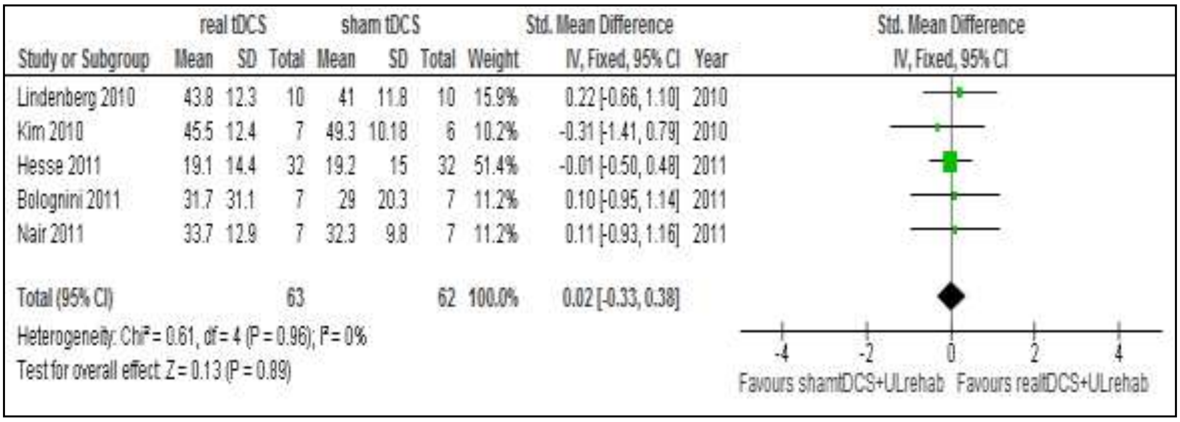

Figure 3.2 Effect of real versus sham transcranial direct current stimulation for upper limb global motor impairments at post-intervention

The same studies except the one of Nair et al., (2011) were pooled in with the follow-up data. The data for the 2-week follow-up was pooled in from the study of Bolognini et al., (2011). A larger non-significant effect size +0.21 was noted at follow-up for UL global motor impairments (Figure 3.3).

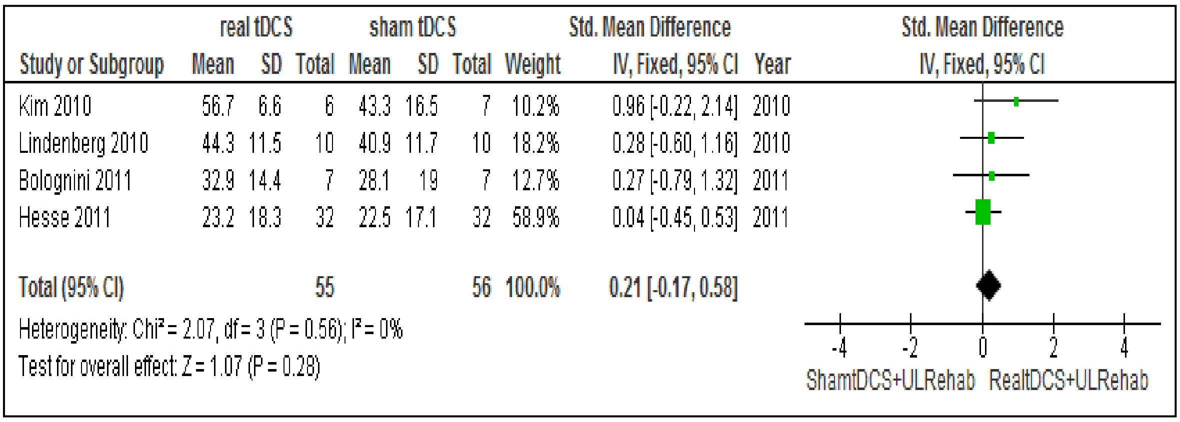

Figure 3.3 Effect of real versus sham transcranial direct current stimulation for upper limb global motor impairments at follow-up

The third meta-analysis involved two studies which explored the effect of anodal tDCS and rehabilitation programmes for the impaired UL in stroke. A small pooled non-significant effect size of -0.06 was obtained favouring sham stimulation and rehabilitation both groups was observed (Figure 3.4). All the participants were in the sub-acute stage in this analysis.

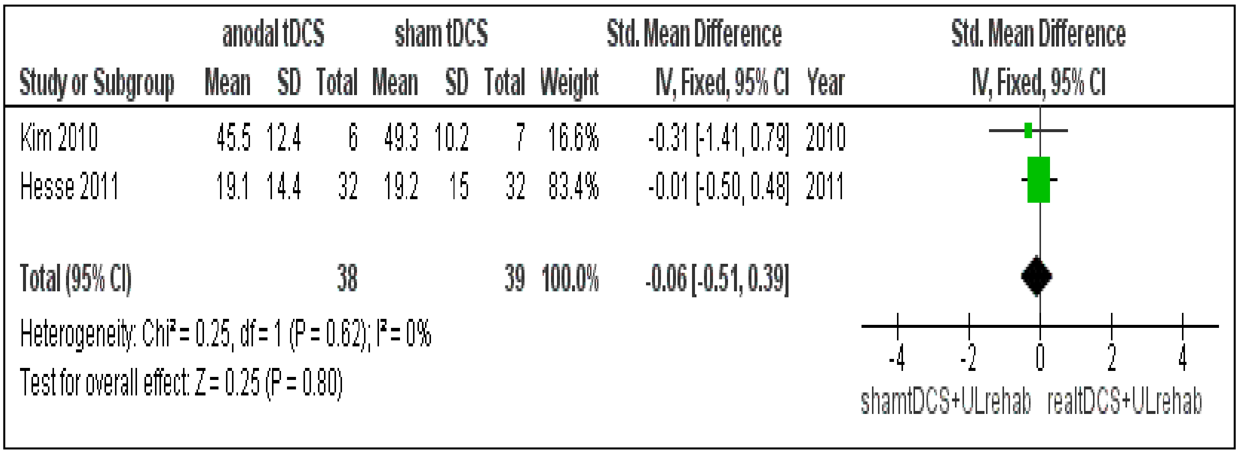

Figure 3.4 Effect of anodal versus sham transcranial direct current stimulation for upper limb global motor impairments

The same studies in addition with the study of Nair et al. (2011) were also pooled in in order to observe the effect of cathodal stimulation versus sham stimulation. One study had to be excluded (Wu et al., 2013) due to use of medians instead of means. The pooled very small non-significant effect size favoured cathodal stimulation 0.03 (Figure 3.5).

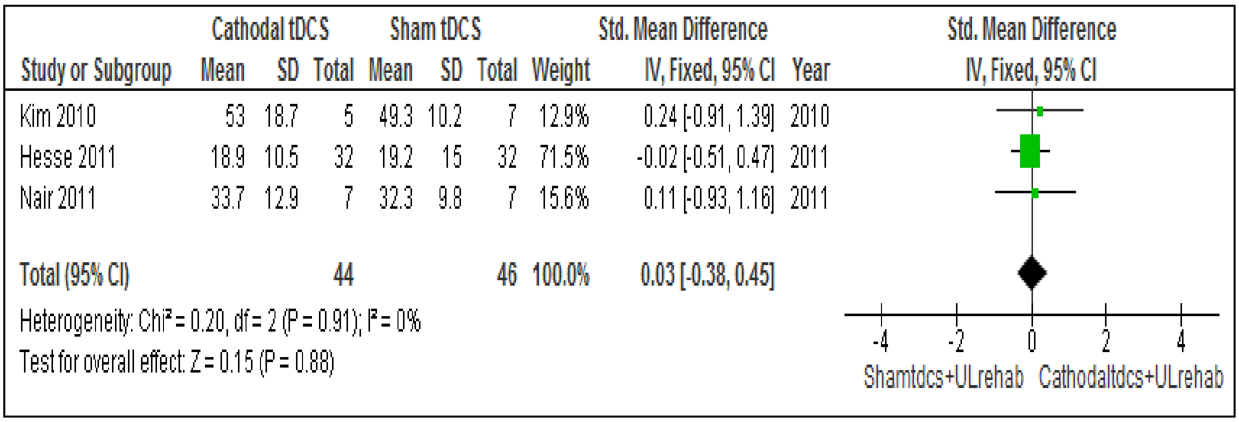

Figure 3.5 Effect of cathodal versus sham transcranial direct current stimulation for upper limb global motor impairments

Two studies using bihemispheric stimulation and UL rehabilitation showed a larger non-significant effect of +0.17 favouring bihemispheric stimulation. In this analysis, all the participants were in the chronic stage of the stroke (Figure 3.6).

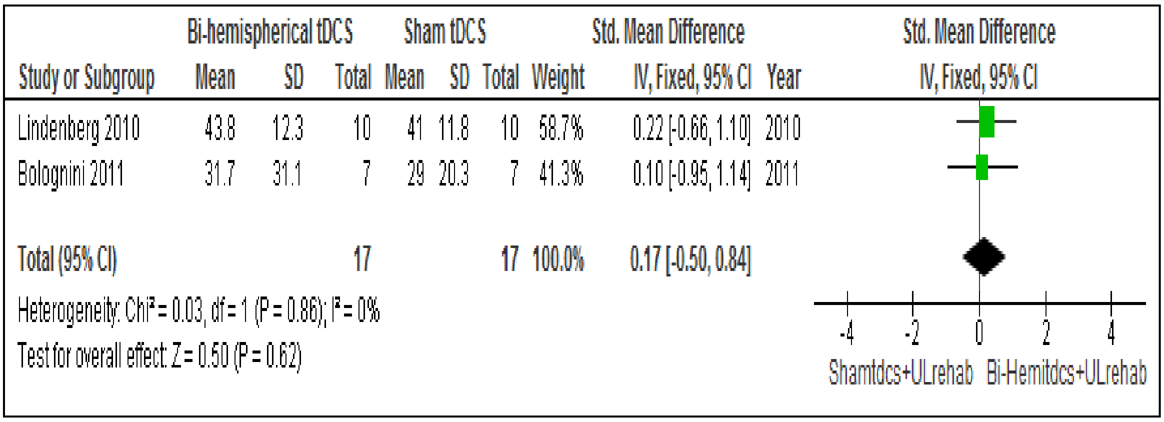

Figure 3.6 Effect of bihemispheric versus sham transcranial direct current stimulation for upper limb global motor impairments

Two studies using bihemispheric stimulation and UL rehabilitation with chronic participants showed a larger non-significant effect of +0.17 favouring bihemispheric stimulation (Figure 3.6).

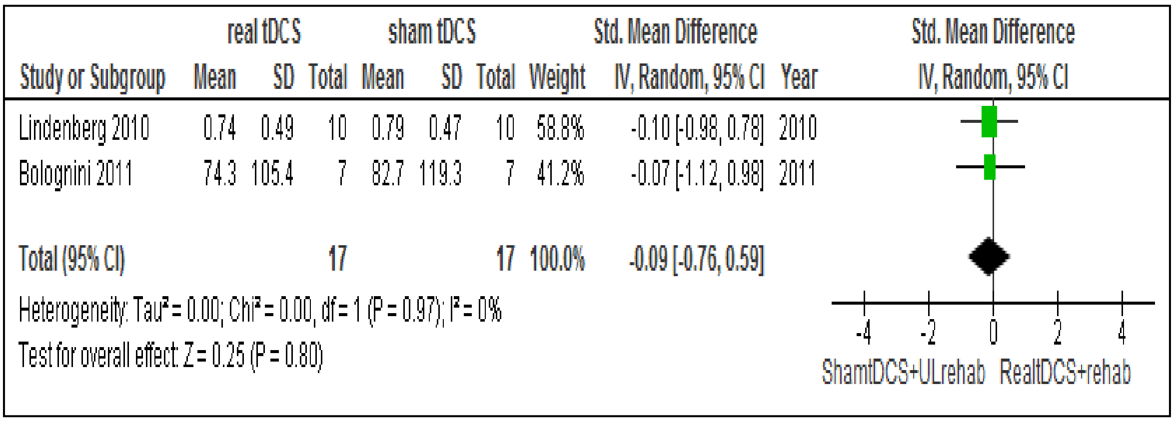

Figure 3.7 Effect of real versus sham transcranial direct current stimulation for upper limb function and dexterity at post-intervention

The next analysis explored the effect of real tDCS and rehabilitation on UL function and dexterity at post-intervention. Two studies using different outcome measures were pooled and a very small non-significant effect size of -0.09 favouring sham stimulation compared to bihemispheric stimulation was reported (Figure 3.7).

3.6.2 The effect of real tDCS versus sham tDCS on activities of daily living

Four studies were pooled in using different outcome measures for the effect of real tDCS versus sham on ADLs. The pooled non-significant effect size was small (0.16) and favouring real tDCS in combination with rehabilitation at post-intervention (Figure 3.8).

	Experimental			Control				Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year
Kim 2010	96.7	8.2	6	69.8	34.4	6	9.0%	0.99 [-0.24, 2.22]	2010
Bolognini 2011	53.6	14.5	32	56.3	15.5	32	56.5%	-0.18 [-0.67, 0.31]	2011
Hesse 2011	2.5	1.3	7	2.5	0.8	7	12.4%	0.00 [-1.05, 1.05]	2011
Khedr 2013	52.1	13.8	14	41.5	13.3	13	22.1%	0.76 [-0.03, 1.54]	2013
Total (95% CI)			**59**			**58**	**100.0%**	**0.16 [-0.21, 0.53]**	

Heterogeneity: Chi² = 5.89, df = 3 (P = 0.12); I² = 49%
Test for overall effect: Z = 0.83 (P = 0.41)

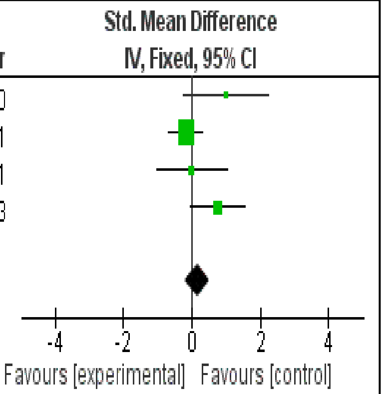

Figure 3.8 Effect of real versus sham transcranial direct current stimulation for upper limb activities of daily living at post-intervention

3.7 Summary of the results

This review has explored the effect of multiple sessions of tDCS in combination with rehabilitation techniques on UL movement and function after a stroke. Only eight studies were eligible for this review demonstrating the paucity of research in this area.

Key findings were that the different tDCS regimes combined with rehabilitation had a very small but non-significant effect size of +0.02 on UL impairment and activity after stroke at post-intervention. At follow-up, a larger effect size of +0.21 was reported for the effect of real tDCS on UL global motor impairments however, the analysis consisted of sub-acute and chronic stroke.

This could be due to the different methodologies, outcome measures, and interventions used in the studies. None of the studies investigated the effect of the intervention on participation, which is an essential component of the ICF framework. Finally, none of the research studies explored the experiences of feasibility of receiving NIBS and RT in stroke.

3.8 Conclusion

From this systematic review and meta-analyses it can be concluded that further research investigating combining tDCS with rehabilitation programmes for the UL in stroke is required. A research study involving one type of tDCS (anodal), in combination with three-dimensional and uni-lateral RT (a technology which none of the aforementioned studies used) for UL impairments of people with stroke is warranted. In addition to measuring impairments and activities, it was established that the effect of the intervention on participation and on the participants' views was also important. The next chapter focuses on the second study: a mixed-methods pilot double-blinded RCT (with a feasibility component) involving people with sub-acute and chronic stroke.

Chapter 4

Pilot Randomised Controlled Trial

4.1 Introduction

This chapter presents the methods, research design and the methodology used for the quantitative and qualitative components of the pilot Randomised Controlled Trial (RCT) with a feasibility component. The research questions for the RCT addressed the feasibility and the effect of combining Robot Therapy (RT) and anodal transcranial Direct Current Stimulation (tDCS) for the impaired Upper Limb (UL) in sub-acute and chronic stroke. The purpose for the RCT was to generate the data required to design a similar RCT with a larger sample. For a pragmatic RCT to be truly effective, qualitative information was also required regarding the participants' views of the acceptability of the interventions. Therefore, a 'mixed methods design' was chosen. A mixed-methods design was chosen because type of research offers a powerful third paradigm that provides informative, useful and balanced results (Johnson et al., 2007).

It was hypothesised that the combination of anodal tDCS and Robot Therapy (RT) results in benefits in UL impairments at post-intervention lasting for three months in sub-acute and chronic stroke. The null hypothesis for this research was that there will not be any differences between real and sham tDCS with RT on UL impairments in stroke. The rationale for the study design is discussed in the next section.

4.2 Pilot double-blinded randomised controlled trial (Quantitative component)

The research design was a double-blinded pilot RCT with a feasibility component.

4.2.1 Aim

The aim of this study was to examine the effect of combining tDCS with RT for the impaired arm and hand for people with stroke.

4.2.2 Objectives

The main objective of this research was to determine the feasibility of the research protocol and to pilot this protocol (the rationale and the reason for piloting the protocol was discussed in Chapter two (Section 2.7). This involved using un-powered, three-dimensional and uni-lateral RT in combination with anodal tDCS for the UL of people with stroke.

The objectives were to:

a) Explore the feasibility of applying anodal tDCS with unilateral and unpowered RT in people with sub-acute and chronic stroke

b) Compare the effect of tDCS and RT with sham tDCS and RT on UL impairments, function, activities and participation after sub-acute and chronic stroke

c) Compare the effect of tDCS and RT with sham tDCS and RT on cortical excitability after stroke

4.2.3 Plan of investigation

A double-blinded protocol was used for this research, with the exception of the TMS assessment which was conducted by Lisa Tedesco Triccas (LTT). The participants and clinical assessors were blinded from the intervention that each participant received (sham or real tDCS). Blinded assessors (Mrs Lindsay O'Connor, Ms Claire Meagher and Mr Seng Kwee Wee) conducted the remaining six of the seven clinical assessments.

The protocol was piloted by LTT and the clinical assessor (Ms Claire Meagher) with one unimpaired participant. This entailed conducting the clinical assessments and measurement of a recruitment curve with Transcranial Magnetic Stimulation (TMS), followed by practice sessions combining the tDCS in addition with the RT.

4.2.3.1 Criteria and recruitment

The following inclusion and exclusion criteria were chosen for the trial.

Participants needed to have:

- 18 years and above
- A confirmed clinical diagnosis of stroke by a neurologist or stroke specialist
- No previous history of another stroke

- >2 weeks post-stroke
- Upper and fore-arm and hand paresis (Medical Research Council scale for muscle strength > 2) with minimal spasticity allowed (Modified Ashworth scale ≤ 2)
- Partial shoulder flexion with gravity
- Good sitting balance; sufficient to maintain sitting posture in an armchair
- Ability to provide informed consent

People with stroke were excluded if they had:

- Impaired gross cognitive function; score of less than 24 of the Mini-Mental State Examination (Folstein et al., 1975)
- Any another neurological condition apart from stroke
- Shoulder pain resulting from shoulder flexion above 90º
- Epilepsy
- Implants within the brain
- Previous brain neurosurgery
- Metal implants in the head including cochlear implants
- Medications that influence cortical excitability
- Previous adverse effects when stimulated with tDCS or Transcranial Magnetic Stimulation (TMS).
- Any chance of being pregnant

Participants taking Selective Serotonin Reuptake Inhibitors were excluded from the TMS assessment due to the increased possibility of an epileptic seizure (Trivedi et al. 2007).

Participants were recruited from the following NHS sites:

- Southampton University Hospitals
- Solent NHS Trust (Early Supported Discharge Team & Community Rehabilitation Team)
- Lymington New Forest Hospital
- Royal Hampshire County Hospital (Winchester)
- Basingstoke and North Hampshire Hospital
- The Royal Bournemouth and Christchurch Hospitals
- St Richard's Hospital, Chichester

In addition, Hobbs Neurological Rehabilitation (a private service) was added to the list of centres to increase the recruitment rate.

Potential sub-acute participants were contacted by their health care professional/ward manager or research nurse on leaving the rehabilitation unit/hospital ward. Participants already in the community were informed about the trial at their home or at the day hospital during their rehabilitation session. People with stroke who expressed an interest in participating in the study were given an information pack which contained a letter explaining the content of the information pack, the participant information sheet, a reply slip (Appendix B.1.1-B.1.5), a prepaid envelope and a DVD. The DVD explained the protocol in a lay format to ensure that the participants were well informed about what was involved in taking part in the trial (Appendix B.1.6).

Following completion of the reply slip by a potential participant, LTT with a letter of access to NHS Sites contacted the participants, ensuring that they fulfilled the inclusion criteria and planned a visit with the participant. The visit took place at the rehabilitation ward or at their home where the study was explained further and any questions were answered. If the participant agreed to take part in the study, LTT arranged an appointment with the participant to visit the lab at the University of Southampton. At the laboratory, LTT confirmed that the participants met the inclusion criteria. If they did not, they were excluded from the trial.

4.2.3.2 Randomisation

Block Randomisation was used. Each participant was randomised into group A or B (Figure 4.1).

- Group A: Anodal tDCS and RT
- Group B: Sham tDCS and RT

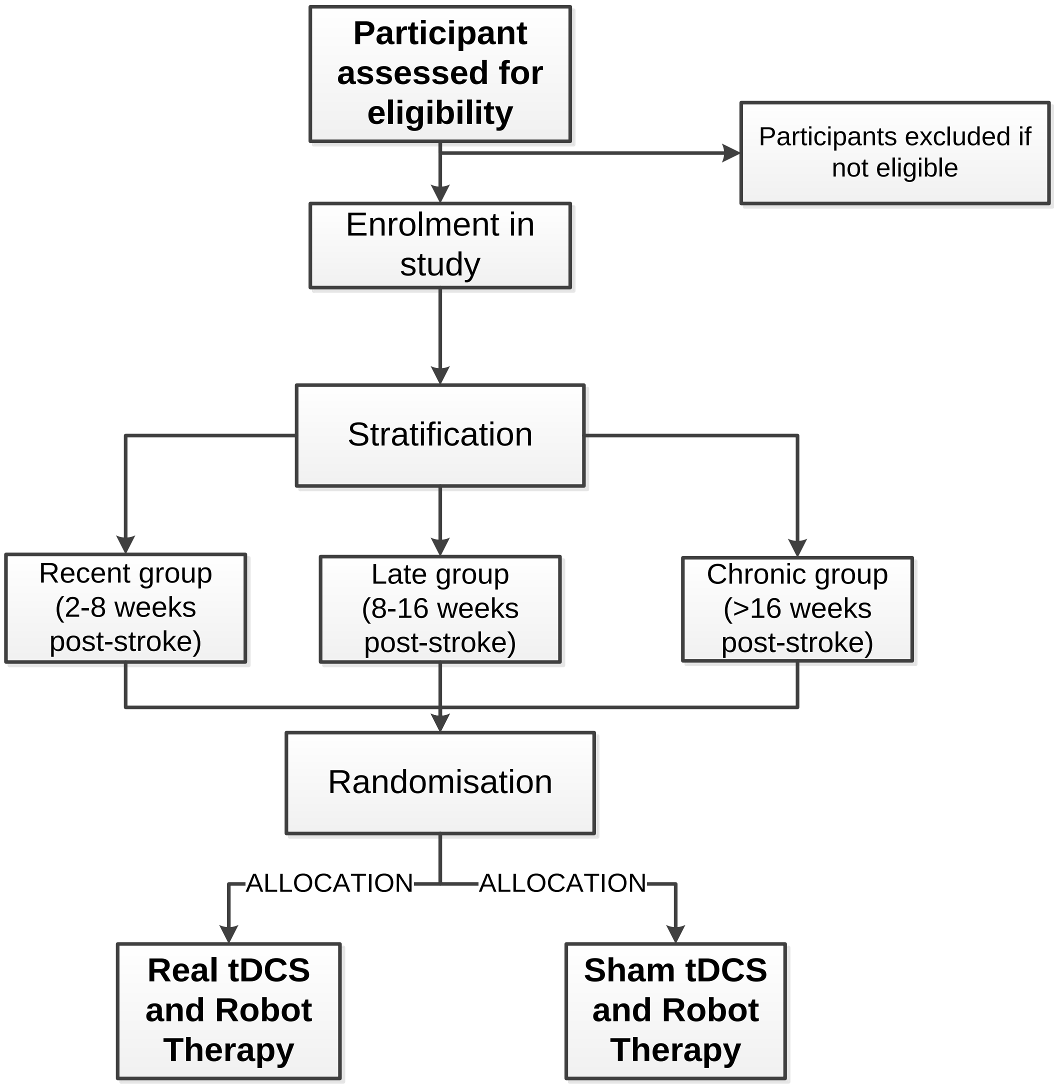

Figure 4.1 Prisma flow diagram: Recruitment and randomisation process of participants into two groups

The first six participants were randomly allocated to groups A or B. Six sheets of paper with an equal amount of either 'sham' or 'real' stimulation were shuffled in a bag by an independent person. This independent person placed the papers in brown envelopes numbered from one to six and sealed. These envelopes were given to another independent person and kept in a locked drawer. As soon as a participant enrolled in the study and fit the inclusion criteria, the main researcher carrying out the intervention made a telephone call to the independent person who stated whether 'real' or 'sham' was typed on the paper. The researcher then applied either 'real' or 'sham' intervention to the participant for the duration of the intervention programme. This procedure ensured concealed allocation.

To enhance the concealed allocation process, after the six participants completed the trial, an external statistician carried out a block randomisation process using a computer program called 'random allocation software' (Saghaei, 2004). The program created blocks of four of either real or sham stimulation. The same independent person from the first stage placed the printed papers of sham/real in sealed envelopes in batches of four.

The participants were stratified into three groups: 'recent' (2-8 weeks post-stroke), 'late' (8-16 weeks post-stroke) and 'chronic' (> 16 weeks post-stroke) (Figure 4.1). The participants in each group were then randomised into the same previous groups:

- Group A: Anodal tDCS and RT
- Group B: Sham tDCS and RT

4.2.4 Protocol

The assessment procedure was always carried out at the laboratory of the University of Southampton. If participants lived close to Southampton, then the intervention procedure was also carried out at the University. If the participants lived closer to Christchurch, then the intervention procedure was carried out at the gym at Christchurch day hospital. Details about the assessment and intervention procedure will be described in the following sections.

4.2.4.1 Assessments

The overview and timing of assessments is presented in Figure 4.2. First, the type of stroke and location of the participant was obtained from the clinicians at the hospital. Screening of the participants was then carried out by Researcher

1. This involved collecting the demographic data including age, gender, disease duration, lesion site and hand dominance. This was followed by assessing cognition using the MMSE (described in the next section) followed by a TMS questionnaire developed by Rossi et al. (2011) to ensure that all the safety guidelines were maintained.

Three blinded assessors also carried out the following clinical assessments which were collected at the research lab at the University pre-, post-intervention and at 3-month follow-up (Appendix E.3 and E.4): The assessors were qualified physiotherapists with experience in stroke assessment and rehabilitation. To ensure consistency, each assessor was trained by LTT how to use the outcome measures.

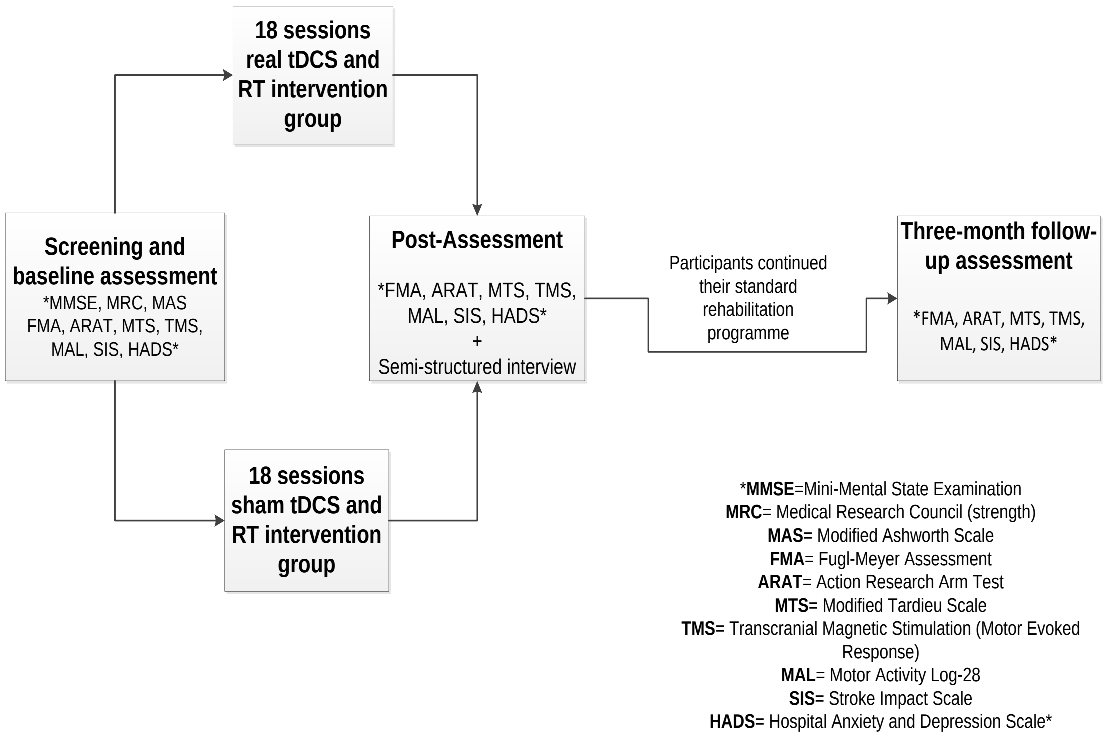

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Figure 4.2 Overview of the timing of the assessments during the randomised controlled trial

This was followed by the measurement of the Motor Evoked Potential (MEP) amplitude and recording the recruitment curve using TMS by LTT. The co-primary outcome measures of this study were the Resting Motor Threshold (RMT) and MEP amplitude and the clinical measure, Fugl-Meyer Assessment (FMA). The secondary outcome measures chosen for this study were the Action Research Arm Test (ARAT), Modified Tardieu Scale (MTS), Motor Activity Log-

28 (MAL), Stroke Impact Scale (3.0) (SIS) and Hospital Anxiety and Depression Scale (HAD). These psychometric properties of these outcome measures were discussed in Section 2.9.

Screening Measures

The Modified Ashworth Scale (MAS) is a single-item measure and describes the resistance perceived while moving a joint through its maximum range. Reflex activity at the lower end of the scale is classified by a phenomenon called a 'catch'. It has a scoring system of zero to five (Bohannon and Smith, 1987).

The Medical Research Council (MRC) strength test is a manual muscle test which uses numeral grades from zero to five (Medical Research Council, 1976). The muscles being tested are graded as follows: Grade 5 is when a muscle contracts normally against full resistance, Grade 4 is when the muscle contraction can still move the joint against resistance but the muscle strength is reduced, Grade 3 is when muscle strength is further reduced such that the joint can only be moved only against gravity when the examiner's resistance completely removed, Grade 2 is when the muscle can move only if gravity is compensated for, Grade 1 is when there is only a trace a flicker of movement observed in the muscle and Grade 0 is when no movement is observed. The chosen screened in this research study were the shoulder flexors/extensors, medial/lateral rotators, abductors/adductors, elbow flexors/extensors, supinators/pronators, wrist flexors/extensors, ulnar/radial deviators and finger flexors/extensors of the affected UL.

MMSE is a screening tool for level of cognitive function and detecting cognitive impairment (Folstein et al., 1983, Dick et al., 1984). The scale contains a series of questions and tests and if answered correctly a maximum score of 30 can be achieved. The scale tests mental abilities, including the participant's memory, attention and language.

Outcome Measures

This section presents the outcome measures used for the RCT.

a) Transcranial magnetic stimulation and neuronavigation

Cortical excitability was measured by using TMS in combination with the neuronavigation equipment and electromyography.

The Magstim® 200[2] single pulse TMS equipment contains a figure of eight magnetic coil attached to the hardware (Figure 4.3). The TMS equipment was connected to the neuronavigation equipment called Brainsight® (CE marked). This neuronavigation system contains a position sensor system which continuously tracks the head location.

Figure 4.3 Magstim Transcranial Magnetic Stimulator with figure of eight magnetic coil attached to the equipment

The Brainsight® consists of a frameless, functional magnetic resonance imaging-guided stereotaxic system with a Polaris Infrared tracker camera (Northern Digital, Waterloo, ON, Canada) and Brainsight® frameless software (RogueResolutions, 2010) (Figure 4.4). This equipment allowed accurate and fast positioning of coils over the cortex, in this case the M1. To measure the MEP response, the TMS equipment was connected to the Electromyography equipment (EMG) developed by Biometrics Ltd. This equipment was connected to a laptop by Bluetooth.

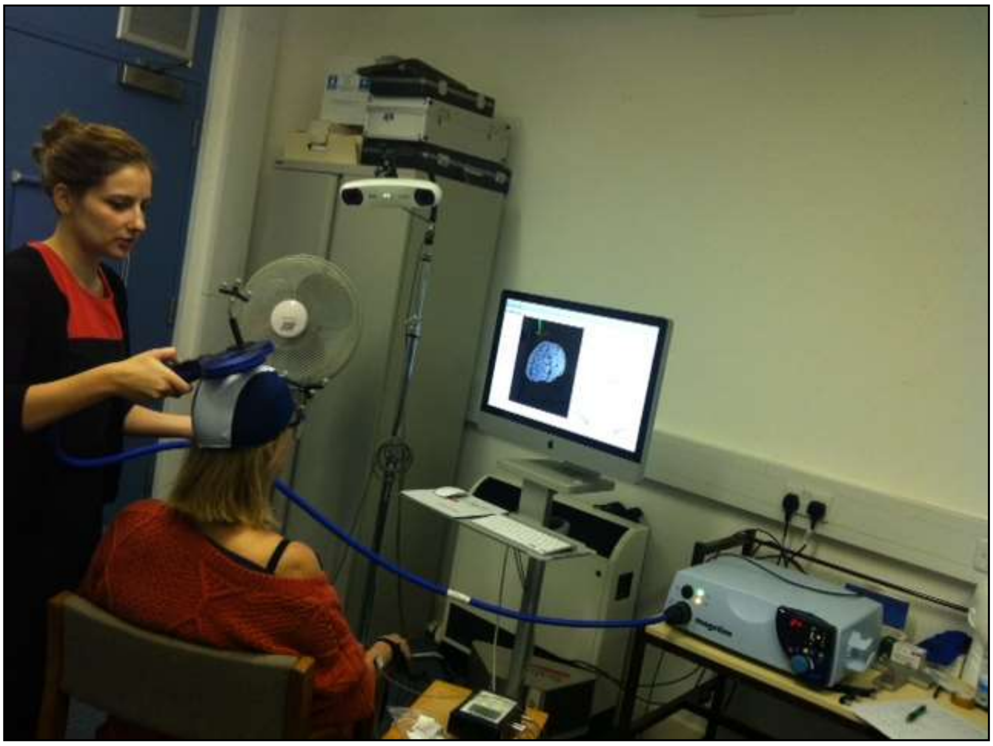


Figure 4.4 Setup of Brainsight® and transcranial magnetic stimulation equipment

b) First clinical measure: Fugl-meyer assessment

The Fugl-Meyer Assessment (FMA) assesses body function and takes around 30 minutes to administer (Fugl-Meyer et al., 1975). The sequence is defined as 1) reflexes reoccur, 2) stereotyped volitional movements can be initiated within flexor and extensor synergies, 3) movements can be performed that deviate from the primitive synergies, and 4) reflexes are normalised. In addition to the score sheet, the measure requires a tendon hammer, a stop watch, a pencil, a tipex tube, a tennis ball and a folded paper. A 3-point ordinal scale needs to be scored to each item of the measure. Score 0) the detail cannot be performed, Score 1) the detail can be partially performed, and Score 2) the detail can be fully performed (Appendix E.4.1). The maximum score for all components of the test is 226. The maximum motor score for the upper extremity is 66 (Duncan et al., 1983). This research explored motor UL impairments and therefore only the upper extremity section was used.

c) Second clinical measure: Action research arm test

ARAT measure consists of a wooden shelf, which is placed on a table in front of the patient, containing blocks and objects of different sizes (Lyle, 1981). This measure is split up into three subtests (grasp, grip, pinch), involving testing the ability to grasp, move, and release objects differing in size, weight, and shape. Objects must be picked up and moved vertically (subtests of grasp and pinch) or horizontally (subtest of grip) to a standardised location (Figure 4.5). Two items in the subtest of grip not only consist of horizontal movement, but also involve a certain degree of vertical movement and pronation of the forearm (pouring water from 1 glass into another) or supination (turning a washer). For the six items in the subtest of pinch, the person is asked to pick up marbles of two different sizes with two fingers only (thumb and index finger, thumb and middle finger, thumb and ring finger, respectively) and move them to a holder on top of the shelf. The fourth subtest consists of three gross movements (move hand to mouth, place hand on top of head, place hand behind head). The quality of the movements per item is rated on a 3-point scale: 0, 1 and 2. The maximum score that can be obtained is 57 (Appendix E.4.2).

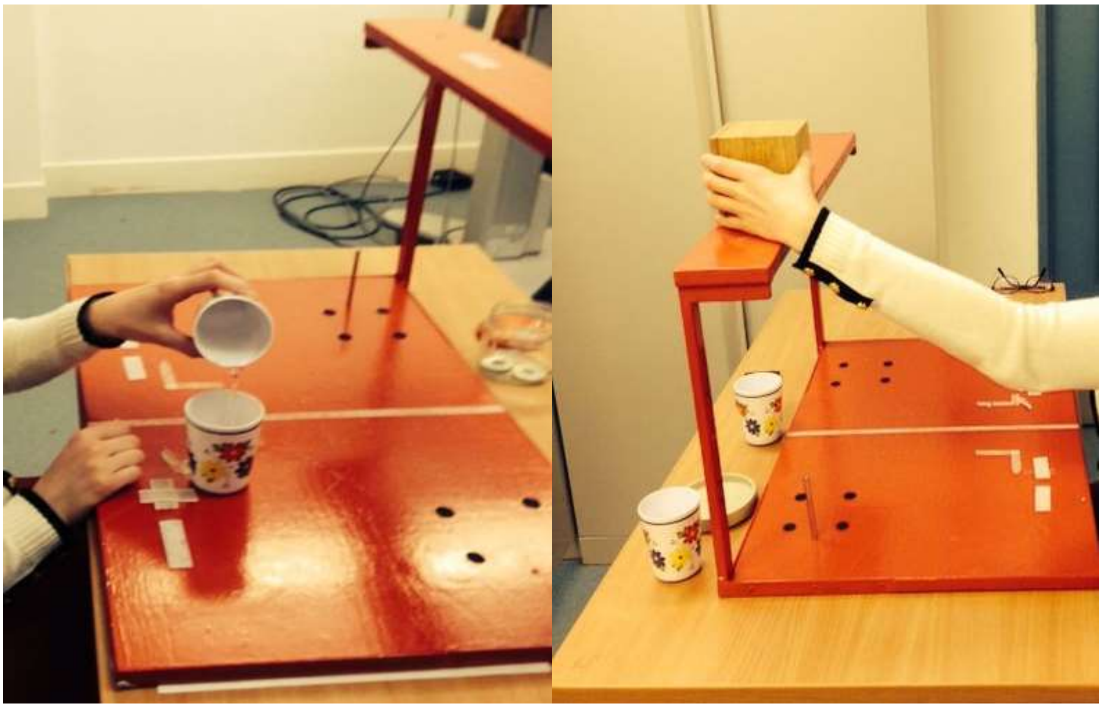


Figure 4.5 A participant conducting the tasks as part of the ARAT outcome measure

d) Third clinical measure: Modified tardieu scale

The MTS is a measurement of impairment and quantifies muscle tone by measuring the intensity of muscle reaction at a specified velocity (Boyd et al., 1999). The assessor does not only take into consideration the amount of resistance at a specific velocity but also at what angle a muscle reaction occurs. This measure involves measuring the quality of muscle reaction between one to five and also the angle of catch of the elbow and wrist flexors during fast velocity of the UL using a goniometer (R1) (Appendix E.4.3). For the elbow flexors, elbow extension was measured. The participant was in sitting with the arm the midline and the forearm in the anatomical position. The goniometer was placed on the lateral epicondyle of the humerus, the stationary arm parallel to the longitudinal axis of the humerus towards the tip of the acromion. The moving arm was placed parallel to the longitudinal axis of the radius pointing toward the styloid process of the radius. For the wrist flexors, wrist extension with fingers flexed was measured also in sitting with the elbow flexed at 90º with forearm in full pronation. The small goniometer was placed on the triquetum hand bone, with the proximal arm placed the ulna bisecting the ulnar styloid, radial head, and lateral epicondyle and the distal arm parallel to longitudinal axis of the fifth metacarpal (Norkin and White, 2009).

f) Fourth clinical measure: Motor activity log-28

MAL registers the use of the paretic hand in daily activities. This measure assesses activity limitation due to impairments in the UL. The MAL is a semi-structured interview during which respondent's rate how well [quality of movement scale (QOM)] and how much [amount of use scale (AOU)] they use their impaired arm during 28 UL activities of daily living (Uswatte et al., 2006). Scores range from 0 (never used) to 5 (same as pre-stroke) and participants may select 0.5 scores (Appendix E.4.4). The summary score is the mean of the item scores (Uswatte et al., 2006, Hammer and Lindmark, 2010).

g) Fifth clinical measure: Stroke impact scale

SIS evaluates function and quality of life in eight clinically relevant domains on the basis of self-report, thus measures participation of the ICF model (Duncan et al., 2003). The SIS (3.0) contains eight domains (59 items), including strength, hand function, mobility, ADL and instrumental ADL, emotion, memory, communication, and participation. The SIS uses the scoring algorithm of the quality of life measure Short Form-36. Each item in each domain is scored on a 5-point scale giving total scores for each domain on a scale from 0 (poorest outcome) to 100 (best outcome). A final question assesses the individual's global perception of the amount of recovery since stroke onset on a visual analogue scale graded from 0 (no recovery) to 100 (full recovery) (Appendix E.4.5).

h) Sixth clinical measure: Hospital anxiety and depression scale

The HAD is a measure of depression and anxiety disorders (Zigmond and Snaith, 1983). The measure is divided into two sections; an anxiety sub-scale: HAD-A and depression sub-scale: HAD-D, with each section containing seven items. The measure contains total scores ranging from 0 to 21 for each subscale and from 0 to 42 for overall distress (Appendix E.4.6).

The permission needed for specific outcome measures were obtained can be found in the Appendix E.4.7.

Preparation for the assessment procedure

Prior to the participants' arrival the equipment was tested and the room was heated to a comfortable temperature. The TMS/neuronavigation equipment was switched on. Batteries of the EMG equipment were tested and replaced if necessary. The preparation of neuronavigation (Brainsight®) involved setting – up the camera, loading the software and calibrating the TMS coil with the neuronavigation equipment . The trackers of the glasses that needed to be worn by the participant were placed on the right if the left motor cortex was stimulated or vice versa. The trackers of the TMS equipment were also adjusted in order to be in view of the camera. The EMG equipment was switched on and connected to the DATALOG software installed to a laptop (EMG software to detect muscle responses). The laptop was placed on the appropriate side of the participant. On the other side of the lab, the equipment for the clinical measures was also prepared. To record the clinical assessments, a video camera was charged and set on a tripod.

Procedure

On the first occasion, the protocol was explained to the participants and informed consent was collected (Appendix D.1 and D.2). This was followed by the screening assessment carried out by researcher 1 (LTT). The blinded assessor then carried out SIS, MAL-28 and HAD measurement on a table in the lab. This was followed by the TMS measurement.

Cortical excitability was measured by using TMS in combination with the neuronavigation and EMG equipment.as shown in Figure 4.10. The participant sat in a chair or remained in their wheel-chair in front of the Brainsight® (RogueResolutions, 2010). The participant was in sitting throughout the whole procedure. It was ensured that the trackers of the Brainsight® glasses and the TMS coil were facing the camera. A material cap was placed on the participant's head by the researcher and the participant then wore the Brainsight® glasses (Figure 4.6). Tape strips were placed on the appropriate side of the participant's head, according to their hand dominance. To prevent any interference, any metal or mobile phones were moved away from the equipment. The Brainsight® was set-up to the TMS coil and registration of the participant was then carried out by the researcher with assistance from the clinical assessor/research assistant. Registration, involved using the pointer to register five specific points of the participant (Figure 4.6). The five points selected were:

- Right ear
- Left ear
- Nasian (bridge between eye brows).
- Tip of nose
- Right eye

Figure 4.6 Researcher placing the pointer on one of the five points on the participant's face

After registration, the TMS coil was calibrated with the Brainsight® equipment by the researcher. Surface Electromyographic (EMG) recording was then set-up to record the activity of the Anterior Deltoid (AD) (proximal muscle) and Extensor Digitorum communis (ED) (distal muscle) muscles in response to TMS. The EMG DataLOG Bluetooth® (Type number W4X8) equipment (Biometrics Ltd) (Figure 4.7) was connected to the program on the laptop and the TMS equipment.

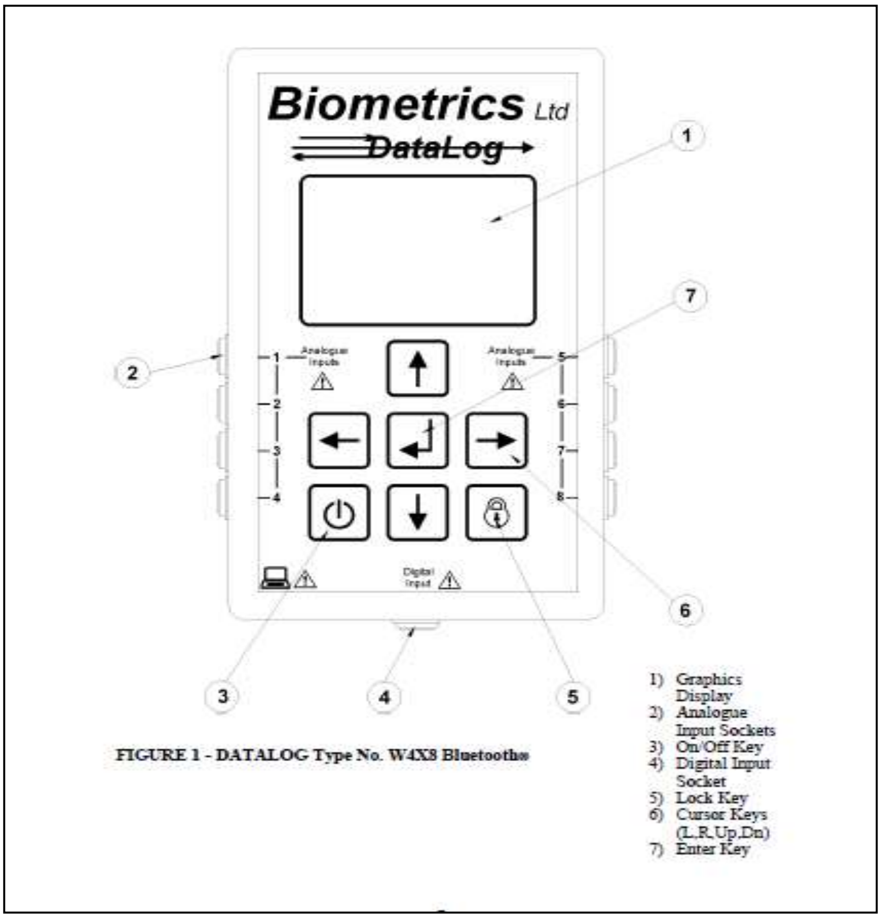


Figure 4.7 Biometrics DataLOG Bluetooth®

Before, attaching the electrodes, the skin was cleaned and wiped with an alcohol swab. The muscles on the participant's arm were located according to the Seniam Guidelines (Hermens et al., 1999). The AD was located by placing one finger width distal and anterior of the acromion. The electrode was orientated in the direction of the line between the acromion and the thumb (Figure 4.8). The ED was located by palpating the lateral epicondyle of the humerus and the styloid process of the radius and ulna and a mark was placed between the two points (Figure 4.9) (Zipp, 1982). Two SX230FW electrodes (with 1000 gain) were placed using a sticky pad on the marked muscle bellies of the affected limb. The reference electrode was placed around the wrist. The leads from the electrodes were attached to the Anologue input sockets of the EMG equipment (Figure 4.7). The computer was switched and the DATALog program was opened. The EMG was switched on via Bluetooth and registered to the computer. The activity of the muscles was checked during voluntary movement of the UL of the participant.

Figure 4.8 (Left) Anterior deltoid skin markings (Right) Electrode position

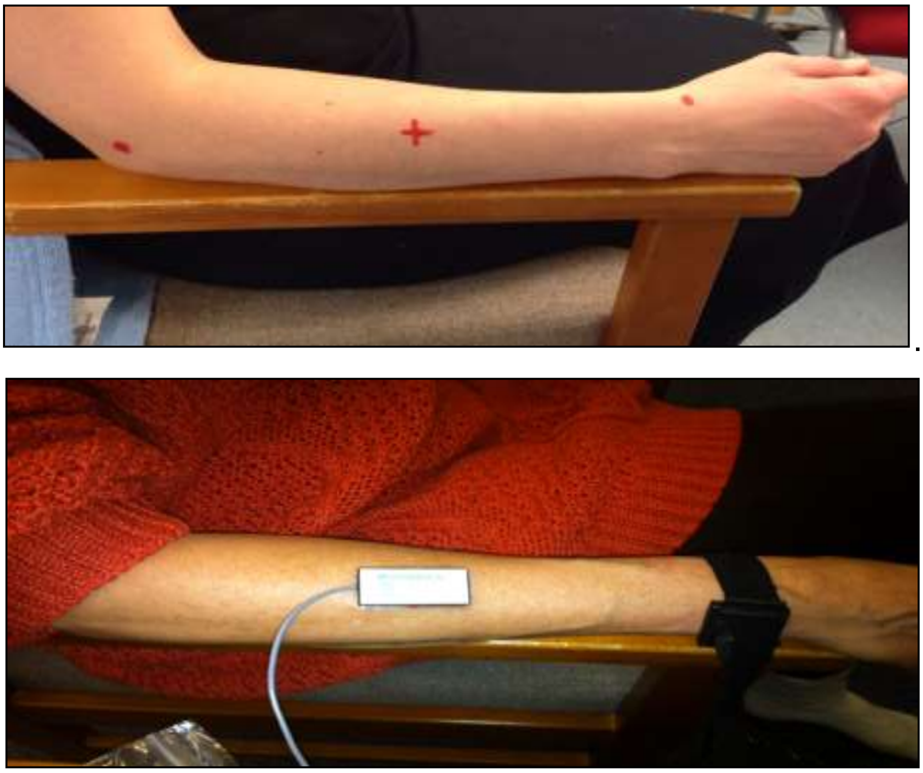


Figure 4.9 (Top) Extensor digitorum skin markings (Bottom) Electrode position

The TMS equipment was then switched on. This was followed by locating the motor 'hot spot' to obtain a MEP by the researcher. The TMS figure of eight coil was placed above the participant's head at a 45° angle in a posterior-anterior plane (Figure 4.10).

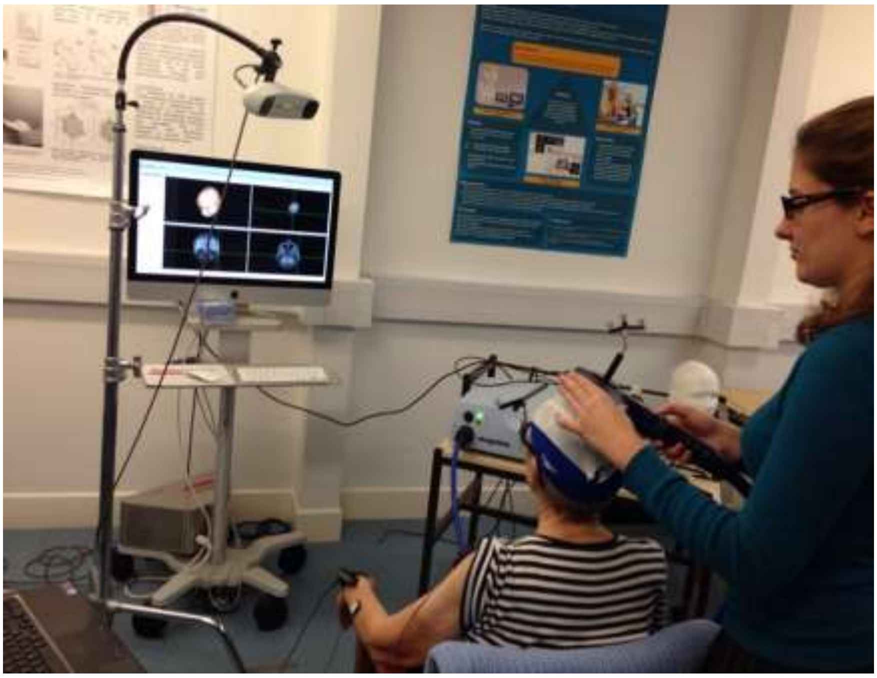


Figure 4.10 Set-up of the participant with the Brainsight®, TMS equipment and EMG

A single pulse of magnetic stimulation was delivered to the M1 of the dominant hemisphere by the coil, every five to ten seconds until a MEP of the AD and ED muscles was noted on the DATALOG program on the laptop.

The minimal intensity to result in an increase of MEP amplitude of 50 μV (as real time) was recorded at the RMT. The 'hot spot' was recorded on the Brainsight® database and measured using a measuring tape. The MEPs was recorded from 90-150% of RMT to measure the recruitment curve of the AD and AD muscles at an interval of 4-5 seconds (Kujirai et al., 1993) (Figure 4.11). The recruitment curves were measured by using a stimulation intensity that was changed systematically in steps of 10% of the individual's resting motor threshold of the anterior deltoid and extensor digitorum communis muscles. Stimulation intensity ranged from 100% to 150%. To optimise accuracy, the TMS coil was placed on the head in the same location for all the measurements by using the Brainsight®.

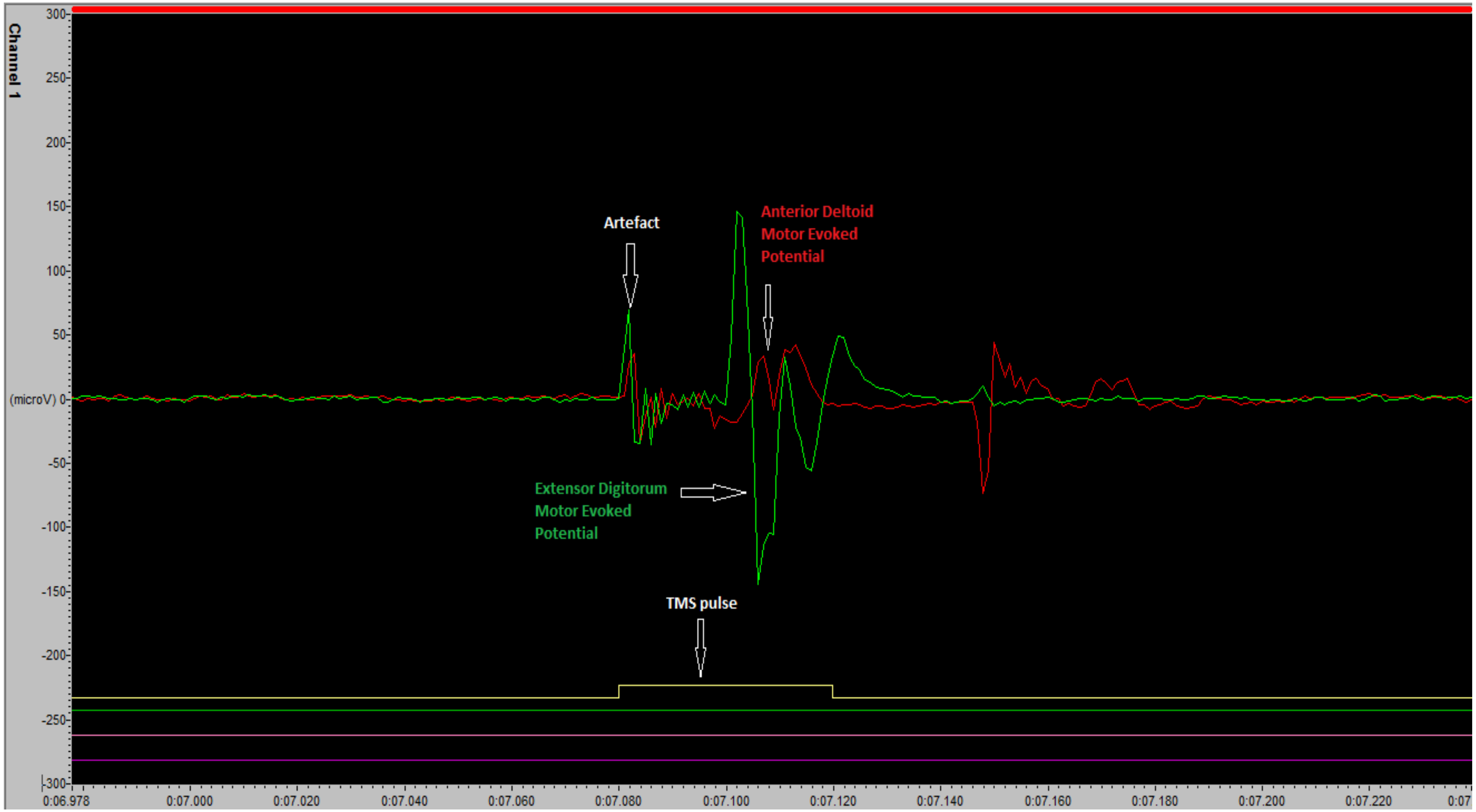


Figure 4.11 Example of a MEP responses from the anterior deltoid (red) and extensor digitorum muscles (green) on DataLog software

The TMS coil was placed on same location of the motor area for the post-intervention and follow-up measurements by using the Brainsight®.

The blinded assessor then carried out the FMA, ARAT and MTS outcome measures. Pictures and videos were taken of the participants during the assessments and intervention sessions. The pictures were taken for documentation purposes and dissemination of the results. The videos were taken primarily in order for an independent researcher (also a clinician) to score the FMA, and ARAT measures by watching the videos. Refreshments were provided when needed. The same assessment procedure was carried out for the baseline, post-intervention and three month follow-up.

If the participant satisfied all the selection criteria completed at the baseline assessment and was willing to enter the trial they were given an appointment for their first intervention session at the Laboratory of the University of Southampton or the gym at the Christchurch Day hospital.

4.2.4.2 Intervention

This section describes the equipment that was used for the intervention followed by the preparation and administration of intervention.

Equipment

a) Transcranial Direct Current Stimulator

The HDCkit® is a tDCS stimulator developed by an Italian company called Newronika™ (Newronika, 2012) (Figure 4.12).

Figure 4.12 Newronika^{TM} tdcs stimulator

(Image courtesy of Newronika^{TM}, Italy)

This equipment includes ‘real’ and ‘sham’ stimulation settings, with an amplitude range of 0.5mA to 1.5mA. The settings can be set by attaching the stimulator to the tDCS programmer by a cable. Sham tDCS conditions are indistinguishable from anodal tDCS conditions (Gandiga et al. 2006). When attached, the duration of stimulation, intensity and type of stimulation can be selected. Electrodes placement is dependent on the choice of stimulation. For anodal stimulation, the anode (red electrode) was situated over the M1 area of the primary motor cortex of the participant’s affected hemisphere (Figure 4.13). If a MEP was elicited during the TMS assessment, the anode was placed on the hot-spot. Additionally, arbitrary positions C3 and C4 of the 10-20 EEG system (Klem et al., 1999) were also measured for the placement of the anodal electrode over the M1 as carried out in previous tDCS studies (Vines et al., 2008, Hesse et al., 2011). This ensured correct position of the anode on M1. The cathode (black electrode) was positioned on the contralateral supraorbital region.

Figure 4.13 Displaying the position of the electrodes with the tDCS stimulator

b) Armeo®Spring robot

The Hocoma[AG] Armeo®Spring arm robot is a commercially available device which facilitates intensive task-oriented arm rehabilitation The robot is an ergonomic arm exoskeleton with integrated springs and provides support for the arm against gravity (Hocoma, 2012). The Armeo®Spring allows variable levels of support against gravity and also provides a large three Dimensional workspace. The robotic arm has integrated sensors that measure kinematics (motion) (Figure 4.14). This allows users to interact with therapeutic computer games and receive feedback about performance (Housman et al., 2009).

Figure 4.14 Armeo®Spring robot at the data collection setting

The robot can be personalised to meet participants' requirements (e.g. side of paresis, body size, level of paresis, and height of support). It contains two springs, one for the upper arm and one for the lower arm.

Figure 4.15 Left Image displays the upper robotic arm settings and right image displays the lower robotic arm settings

The upper arm can be adjusted from the maximum to minimum tension levels (Level A-K respectively) for participants with mild impairments to severe impairments. The lower arm can be adjusted from scale one for participants with severe impairments to scale five for participants with mild impairments (Figure 4.15).

Preparation

Prior to the arrival of the participant, the lab or the gym was set-up. The equipment was tested and the room was heated to an appropriate temperature to ensure participant comfort. The tDCS equipment was set on the sham or real setting after using the code to start up. The Robot database was switched on and robot settings were updated. According to the FMA baseline score, the robot spring settings were set as explained in Table 4.1.

Table 4.1 Armeo®Spring assessments for different upper limb impairments

Assessment	**Mild UL Impairment (FMA[*1]=50-66)**		**Moderate UL Impairment (FMA[*1]=20-50)**		**Severe UL Impairment (FMA[*1]=0-20)**	
A-Goal and Vertical Catching	*Level of Support*	*Difficulty Level*	*Level of Support*	*Difficulty Level*	*Level of Support*	*Difficulty Level*
	Upper Arm: Level C[*2]	Hard	Upper Arm: Level F[*3]	Moderate	Upper Arm: Level J[*4]	Easy
	Lower Arm: Level 4[*2]		Lower Arm: Level 3[*3]		Lower Arm: Level 2[*4]	

[*1]FMA=Fugl-Meyer Assessment, [*2] Minimal support by the robot, [*3] Moderate support by the robot, [*4] Maximal support by the robot

The robot was moved to the left or right according to the side of impairment of the participant.

Administration of Intervention

The intervention programme comprised 18 sessions during an eight-week period (approximately two sessions per week). TDCS / sham tDCS was applied for the first 20 minutes of the one hour RT training session. During the training session, resting time was predetermined, or as frequently as the participants needed. Each treatment session took approximately an hour and 15 minutes in total. When the participant gave full consent, the first RT and tDCS session was carried out either on the same day as the assessment session or in the next few days. This was dependent on the level of fatigue expressed by the participant after the baseline assessments. Participants visited the lab for a total of 21 sessions including 18 intervention sessions and three assessment sessions.

Procedure for the Armeo®Spring RobotTherapy

Each participant was invited to sit in a normal chair with a back support or use their own wheel-chair. Their affected arm and hand was positioned in the robotic device (Figure 4.16).

Figure 4.16 Arm and hand positioned by velcros on the robot arm

The robotic arm was set up according to the arm length of the participant. The grip module was also adjusted in order for the participant to grip at a comfortable mode during the session (Figure 4.17).

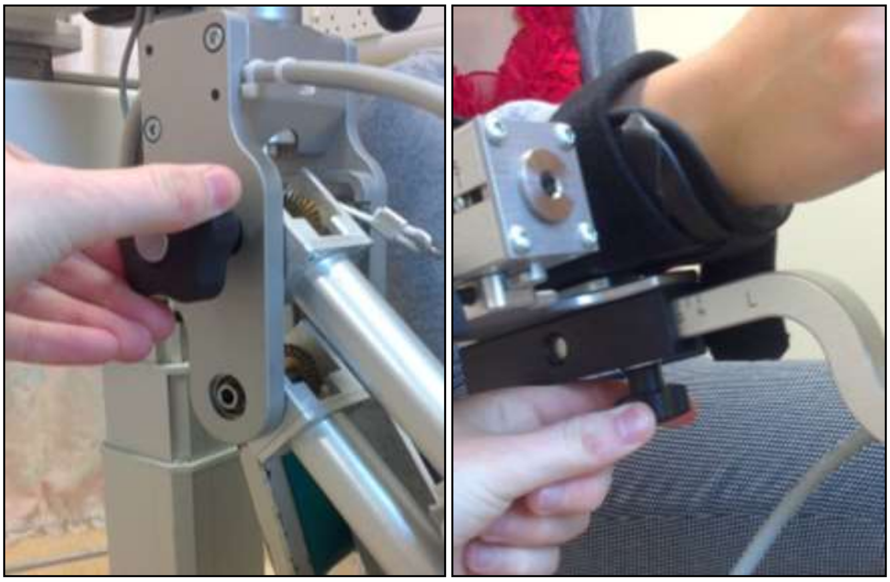
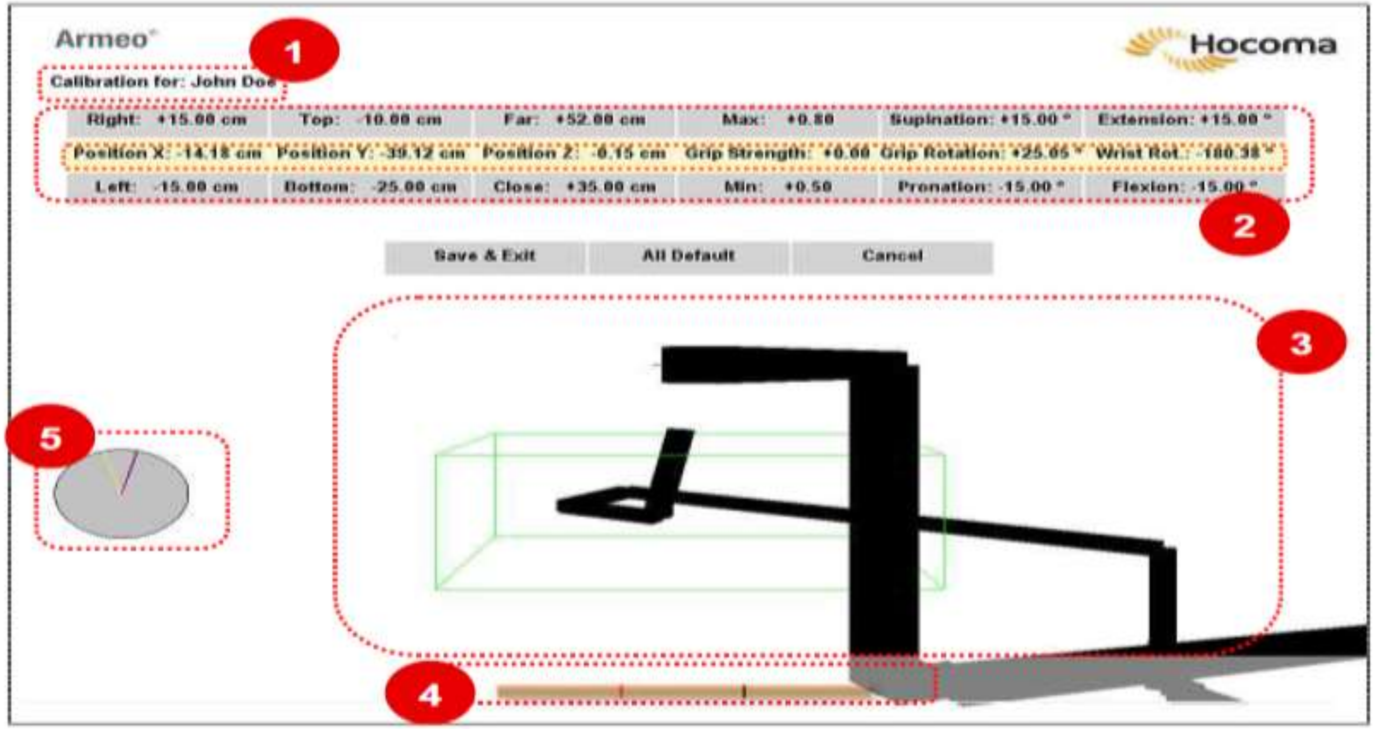


Figure 4.17 Setting the length of the robotic arm by using a screw (left) according to UL length of the participant

In front of the participant, there was a computer screen which was connected to the robotic device (Figure 4.21). After the robot was set up and the participant was comfortable, the ‘work-space’ was set on the computer (Figure 4.18). This ensured that the video games are mapped into a cubic workspace which were adjusted to the movement abilities of each participant.

This involved the participant moving the robotic arm to the left and then right (shoulder abduction and adduction), then lifting up and pushing it down (shoulder flexion and extension), bringing the lower part of the arm close to the participant’s abdomen (elbow flexion) and then straightening the lower part (elbow extension) and then pronation and supination of the grip module. These movements were carried out as maximal range. This was followed by the participant gripping the grip module of the robot at maximum power. These settings were recorded at every session.



1) Displays the name of the participant whose settings are going to be customised
2) Current values of the upper limb's end position in cm, pronation/supination in degrees and the grip strength in arbitrary units are displayed in the yellow box
3) Arm model/Current range of motion: The robot arm is shown in its current position as a beam model. The workspace is depicted as a box who size represents the current range of motion
4) The brown coloured bar shows the current grip strength
5) This shows the range of motion of the forearm (pronation/supination)

Figure 4.18 Setting up the UL work-space on the Armeo® robot

By moving their UL, they were then able to carry out two assessments at the beginning of every session. The first assessment was called ‘vertical catching’ and this involved a lady-bird appearing on the screen and by moving the robotic arm the participants were able to hit the lady-bird with the target. The kinematic measurements of the shoulder and elbow joints and the hand path ratio (distance between the cursor and the target which is calculated the length of the pathway divided by the straight line distance) were then saved on the computer (Figure 4.19).

Figure 4.19 Vertical catching assessment of the Armeo® robot

The cursor (circle on this picture) had to be placed over the lady-bird (target) with the robotic arm by the participant until the next lady-bird appeared on a different part of the screen

The second assessment was called the ‘A-Goal’. Participants had to guide the ‘cursor’ to a home-base. A target then appeared on the screen and the participants had to reach it by moving their arm (with the robotic arm) and try to follow a straight line. The participants kept their arm in that position until the target disappeared from the screen and then returned the cursor back to home base (Figure 4.20). The two assessments were carried out at the beginning of the session without the tDCS stimulation. The assessments measured the hand path ratio and kinematic angles of the shoulder and elbow joints.

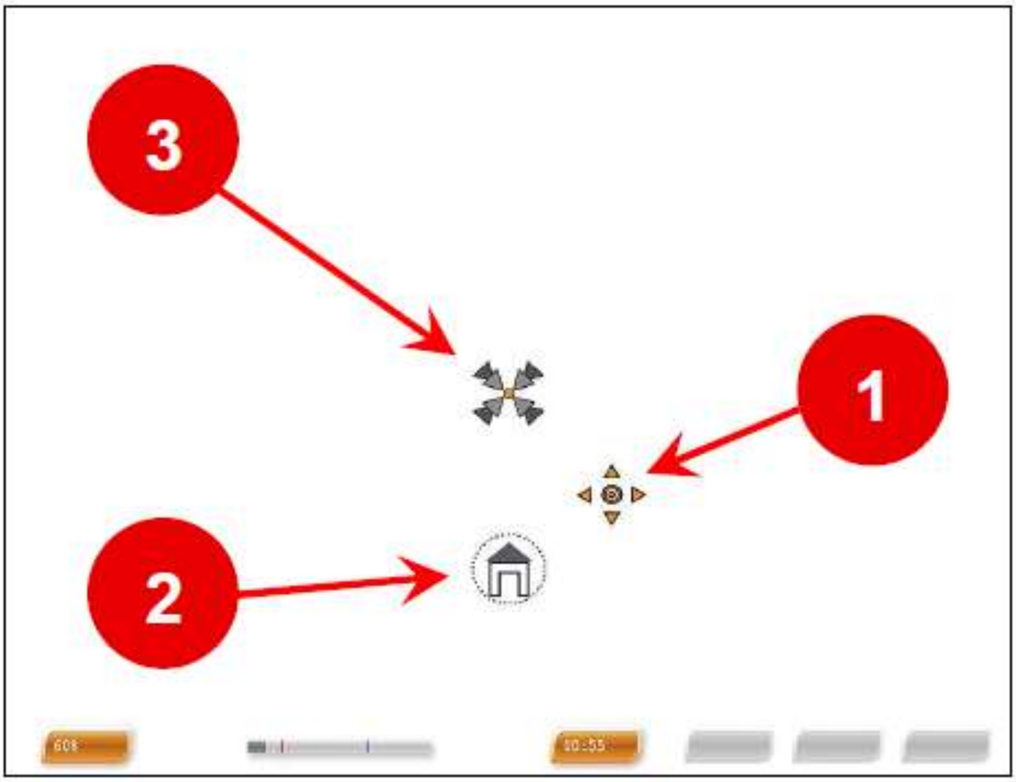


Figure 4.20 ‘A-Goal’ assessment on the Armeo® robot

(displaying the (1)‘cursor’, (2) ‘homebase’ and (3) ‘target’ positions)

After the assessment the tDCS was applied (this is be explained in detail in the next section) high-intensity, repetitive movements directed by the video games demonstrated on the computer screen were carried out by the participant for approximately an hour (Figure 4.21).

Figure 4.21 A lady playing a computer generated fruit shopping game using the Armeo®Spring Robot

(In the game, the person needed to manoeuvre the robot to pick up an apple and place it in the shopping cart as demonstrated on the computer screen)

The first three games of the robot treatment programme were always the same; a) water drop catching with a mug, b) fish catching c) fruit shopping. Participants then chose whichever games they wanted to play e.g. shooting chickens or car racing as displayed in Figure 4.22.

Training targeted integrated movements involving the shoulder, elbow and wrist of the impaired UL. The games and the rest intervals were determined by clinical need – the participants were given games that challenged them, but allowed them to achieve a minimal score e.g. 10%, to ensure they did become demotivated**.** The games also depended on personal preferences and would be changed if the participant did not enjoy a game. More able participants carried out more challenging games. Participants who fatigued easily were allowed more resting time. The aim was that after each session, the level of support was minimally decreased in order to encourage maximal effort by the participant.

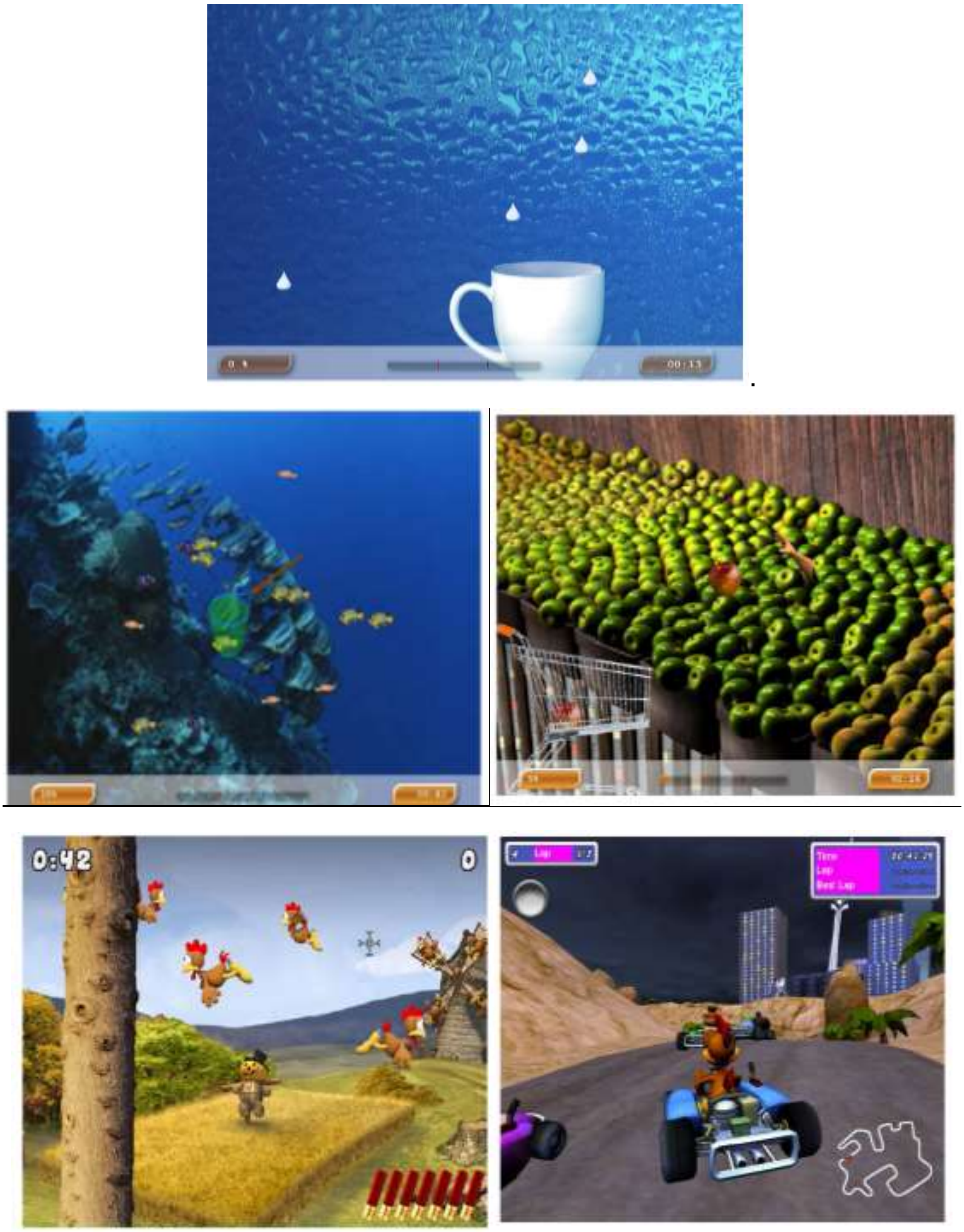


Figure 4.22 Selection of video games used for the RT programme

<u>Procedure for application of tDCS</u>

Anodal tDCS was administered using the CE marked transcranial Direct Current Stimulator (Newronika™ Italy). Direct current was transferred by 35 cm^2 (7x5cm) rubber electrodes surrounded by saline-soaked pair of surface sponge electrodes. The step by step procedure of tDCS application as follows:

a) The sponge bags (one pink for the anode and blue for the cathode) were soaked in 2ml saline solution (Normasol 0.9%) ten minutes before each intervention session.

b) The skin on the areas to be stimulated was cleaned with water and then dried. The skin was also checked for any abrasions.

c) The correct placement for the anode electrode on M1 was registered during the assessment procedure if a MEP was evoked. This was recorded and it was ensured that the anode was located on the same specific area during each session. As previously described on page 111, the C3 (if stimulated on the left M1) or C4 (if stimulated on the right M1) position was located with a tape measure in centimetres (Figure 4.23). The distance between the nasion (bridge of the nose) and inion (occipital protuberance) was measured. Half of this length was then measured on the participant’s head using a non-permanent marker (sagittal point).

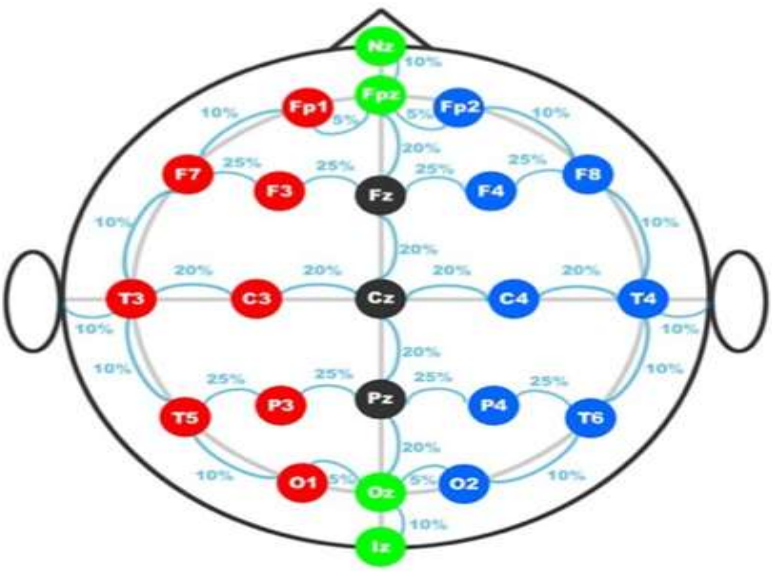


Figure 4.23 EEG markings of C3 and C4 positions on the head

(Klem et al. 1999)

The distance between each pre-auricular point (the indentation above the zygomatic notch) was then measured. Half of this total was measured which met the point previously measured (middle point). The distance from the middle point (Cz) to the pre-auricular point was measured and a 10% point was marked as (T3) (left) and T4 (right) positions. The distance between the T3 and T4 positions to the middle point was measured and 50% of this measurement was marked as C3 or C4 accordingly.

d) The rubber electrodes were then placed in the sponge bags. The red cable was attached to the anodal electrode and the black cable was connected to the cathodal electrode (Figure 4.24). In order to increase conduction, in some cases conductive gel was applied to the outer surface of the sponges

Figure 4.24 Rubber electrodes ($35cm^2$) placed in the sponge bags and connected the HDCstim

e) The anodal tDCS (red electrode) was applied over the M1 area of the affected hemisphere. Stimulation was applied at an amplitude of 1mA.The cathode was positioned on the contralateral supraorbital region (blue electrode) using an adhesive bandage (Figure 4.25).

Figure 4.25 Participant with the attached tDCS electrodes whilst carrying out RT

f) The leads were connected to the HDCStim and switched on (programmed in sham or real setting before the participant arrived).

The tDCS remained on for 20 minutes for the anodal tDCS session. The tDCS stimulator has an integrated sham option where the direct current in this option was switched off after 10 seconds, thus the participant felt the initial sensation but did not receive current for the rest of the stimulation period. In all cases, the current faded-in and faded-out over 10 seconds at the beginning and end in a ramp-like fashion so that unpleasant sensory side effects could be minimised.

Once the participant was comfortable, the stimulator was switched on and the participants were asked to perform the set of games for an hour. After 20 minutes, all non-invasive brain stimulator equipment was switched off and the participant had a break from the RT. After the break the participant continued the robot session for around 30 minutes.

4.2.5 Monitoring safety and adverse reactions

As part of the feasibility study, safety and adverse reactions were monitored throughout the assessment and intervention sessions.

4.2.5.1 Monitoring during the Assessments

Safety guidelines published in 2009 by the Safety of TMS Consensus Group (Rossi et al., 2009). These guidelines state that the only absolute contraindication to TMS is the presence of metallic hardware in close contact to the discharging coil. Examples of this are cochlear implants, an internal pulse generator or medication pumps). Therefore, people with such a condition were excluded from the study. Also a questionnaire was used as a screening procedure before TMS was applied (Rossi et al., 2011) (Appendix E.3.3).

Recruited participants were informed of any possible side effects that could occur (described in sub-section 2.5.1.2). The researcher asked the participants at the beginning and end of every session whether they had experienced any side-effects (Appendix F.1). In the case of adverse reactions, the situation was assessed by the researcher and the Experimental Officer (also the Faculty Health and Safety Officer). Medical advice was also obtained by consultation with the neurologist related to this research project, Dr. Desikan, based at the Institute of Neurology, UCL, London.

<u>Monitoring during intervention</u>

Case record forms were filled in at the beginning of every intervention session (Appendix F.1). Skin condition was visually inspected before and after tDCS. After each tDCS intervention session, all participants were asked to report their experiences of the sensations related to tDCS by completing a survey (Fertonani et al., 2010) (Appendix F.2).

Additionally, as part of the feasibility any adverse reactions and safety issues were also reported in the semi-structured interviews (discussed in the next section).

4.3 View and experiences (qualitative component)

Participants were interviewed at the post-intervention assessment in order to explore their views and experiences from taking part in the trial. The aim of this component is to obtain the perceptions about the feasibility of Non-Invasive Brain Stimulation (NIBS) and RT as a rehabilitation technology for people with sub-acute stroke.

4.3.1 Objectives

The objectives were:

- To explore the views and experiences about NIBS
- To investigate what people with felt about the RT sessions and its effects on the UL
- To explore the advantages and disadvantages of both technologies

4.3.2 Study design

A qualitative interview approach combining structured and semi-structured interview questions was used. The interviewer had a structure to follow and collected all important information, however, allowed participants to express their own thoughts and feelings (Holloway 2008). Interviews were carried out by an external psychologist (Dr Katie Meadmore [KM]) who was independent from the trial.

4.3.3 Protocol

Semi-structured interviews were carried out after the post-intervention clinical assessments at the Laboratory or at the participants' home. The participant with stroke completed a separate consent form (Appendix D.3). A digital audio recorder was used to record the interview and field notes were taken by KM during the interview which lasted between 20-40 minutes. A guide was followed for each interview which can be found in Appendix G. In general, there were two people in the room, KM and the participant. Sometimes the carer of the participant remained in the room; however, they were not involved in the interview. The first interview was considered as a pilot interview and from this interview, the interview guide was changed accordingly.

4.4 Ethical considerations

Ethical Approval was sought from the Hampshire NHS Research Ethics Committee (REC) on the 30th August 2011 (Appendix C.1). An IRAS form, as well as supporting documents were submitted to the REC. The principal investigator Professor Jane Burridge and LTT attended the meeting. Any questions were answered, followed by a favourable opinion with minor amendments. The amendments were accepted by the chair of the REC (Appendix C.2). This process was followed by seeking Research and Development (R&D) approval from five different NHS sites.

R&D approval was obtained from the following NHS Sites:

- University Hospital Southampton NHS Foundation Trust
- Solent NHS Trust
- Hampshire Hospitals NHS Foundation Trust
- Southern Health NHS Foundation Trust
- The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust
- Western Sussex Hospitals- St Richard's Hospital

This involved obtaining a research passport and letter of access for researcher LTT in order to access the different NHS sites. Two amendments were submitted to the REC and R&D after the first initial approval. The aim of the first amendment was to increase recruitment. This involved advertising the RCT in local newspapers, and addition of private neurological rehabilitation clinics as recruitment sites. In addition, the first amendment involved the addition of the qualitative component of the research and an additional outcome measure, HAD. The approval letter for this amendment by the REC is found in Appendix C.2. The second amendment involved the change of criteria for the study. Initially the study's main aim was to recruit only people in the sub-acute stage. However, since it was very difficult to recruit people in this stage, the addition of people in the chronic stage was added to the inclusion criteria. Additionally, the upper age limit of 80 years of age in the inclusion criteria was removed and an additional Armeo® Spring robot was transported to Christchurch Day Hospital as an additional data collection site. The second approval letter from the REC can also be found Appendix C.2.

4.4.1 Ethical factors associated with the research

It was ensured that each participant gave written, informed consent for both the quantitative and qualitative components of the research. It was also ensured that any information related to the participants was kept anonymous from external people not involved in the project and confidentiality was also promised throughout the research. Each participant had the option to withdraw from the study at any time.

At the Laboratory of the University of Southampton, (after giving informed consent), participants were confronted with their disability which could have led to psychological distress. The researcher (LTT) who worked on this project is a physiotherapist registered with the UK Health Professions Council. Part of the Physiotherapy programme consisted of dealing with people with long-term conditions and the psychological issues that arise from this. The physiotherapist at the lab (LTT) was well-trained to perform these assessments in a professional manner and provided continuous support when needed. In addition, the physiotherapist had four years' experience working with people with neurological conditions including stroke. When there was any distress in relation to tDCS, LTT stopped data collection and monitored the participant. If the distress continued, the carer of the participant was consulted and eventually, the decision was made whether or not to include the participant in the study. More detail about adverse events can found in Section 4.2.5 of this chapter.

4.5 Overall project funding

This project was partially funded by Wessex Medical Research. This enabled the purchase of the TMS and tDCS equipment and partially funded participant travel reimbursement. The Faculty of Health Sciences provided funding for the researcher (LTT) to disseminate the results at four conferences. Additional funding for participant travel reimbursement was obtained from the Maltese Government and European Union through an organisation called Strategic Educational Pathways Scholarships.

4.6 Data and statistical analyses

4.6.1 Quantitative data analyses

The mean and Standard Deviation (SD) scores for the demographic data were calculated. In addition, the median with minimum and maximum scores of the screening measures were calculated.

The data of the participants with sub-acute stroke, were pooled into one group. Therefore, the data were analysed in relation to two groups: sub-acute (real and sham) and chronic (real and sham). FMA and ARAT data were rated by the clinical assessor and an external clinical assessor. The added scores of each participant were matched and any disagreement was resolved by discussion between both assessors. The quality of movement scores of MAL were added and divided by the number of activities the participant carried out (e.g. 41 [total score]/23 tasks out of 28). The data of the SIS was processed using the equation presented in Appendix E.4.5. The data of the HAD was added according to the allocated points for each domain presented in Appendix E.4.6.

The MEP data was exported from the DATALOG program to a 'txt' file. These files were then inputted into the software program MATLAB R2013b (32-bit). A program was written by the Experimental Office of the Faculty of Health Sciences (Dr Martin Warner) and this program was used to measure the peak to peak amplitude of each MEP. After data analysis was carried out at the TMS Laboratory at the Institute of Neurology, problems were identified with the data. It was noticed that in several participants MEPs were not elicited even at high intensities. Data analysis of the RMT and MEP amplitude was only possible for the ED muscle of five sub-acute participants. The data was inputted into Microsoft Excel 2010 and the mean peak to peak amplitudes of five MEPs TMS intensities from 100 to 130% on the three different occasions were calculated.

The data from the Armeo® was also exported as an Excel file. Data of the HPR, the shoulder and elbow angles of 18 sessions of 16 participants from the 'Vertical catching' and 'A-Goal' assessment was analysed.

The data from the clinical outcomes and Armeo® measures were inputted to IBM SPSS Statistics Version 21. The Kolmogorov–Smirnov test and normality plots on histograms were used to check the normality of the data. Mean and parametric statistics were used if the data was normally distributed; otherwise median and nonparametric statistics were used.

For normal data: two-way repeated measures Analysis of Variance (ANOVA) were used to test the overall effect of the intervention at the three assessment time points. The Green-house Geisser test was used when Mauchly's Test of

Sphericity was found significant. Multiple linear regression was used to test the effect of variables such as real or sham tDCS stimulation on the post-intervention or follow-up data. The basic model chosen was:

$$\mathbf{Y = B_0 + B_1G + B_2P + B_3(G \times Baseline\ Score) + B_4T + B_5C}$$

Y= The Dependent Variable (e.g. post-intervention data)

B_0= Regression value (constant)

B_1G= Type of Group (real/sham)

B_2P= Baseline Score

B_3(G x Baseline Score)= Interaction between the type of group and the baseline score

B_4T= Time since stroke

B_5C= Stroke Location (cortical versus sub-cortical)

For the three-month follow-up, the data were compared with the baseline intervention. The Paired-Samples t-test was used for post-hoc analysis to compare means values between two time-points (i.e. baseline and post-intervention or baseline and follow-up scores). If the data werenot normally distributed, the Friedman ANOVA test was used (i.e. the nonparametric equivalent of the repeated measures ANOVA) to analyse the data at the three time-points, and linear regression was used to examine the effects of the variables on the outcome measure. The Wilcoxon signed-rank test was used for post-hoc analysis in order to compare two related samples at two time-points (i.e. baseline and post-intervention or baseline and follow-up scores). Significant values were accounted at $p = \leq 0.05$. Table 4.7-Table 4.20 and Figure 3.2-Figure 3.8 were plotted displaying the data accordingly.

4.6.2 Qualitative data analysis

For the structured questions, the responses were pooled together and percentages were calculated. For the responses of the semi-structured questions, audio recordings were transcribed verbatim and any identifiable information of the participants was removed from each transcript. The transcripts were analysed using thematic analysis (Braun and Clarke, 2006). This type of analysis involves identifying,and reporting patterns (themes) within data. The transcripts were coded and then themes were generated by LTT. These themes were collated in summary tables and for each theme from the participant's view and experiences were summarised. For the purposes of data verification, the ranges of interpretations were reviewed by an external researcher (Dr Maggie Donovan-Hall [MDH]). The two researchers discussed the emerging themes and reached agreement concerning whether modifications should be made or if any themes should be split, combined or withdrawn. LTT finalised the themes and selected appropriate quotes to support each theme. A possible search for relationships between segments and patterns was also carried out. Table 4.24-Table 4.26 were plotted to show the responses of the structured questions.

4.7 Results - Pilot RCT

The process of recruitment, demographical and screening data, compliance, adverse reactions and concomitant treatment received by participants during the trial are presented. Results of the clinical and neurophysiological measures at baseline, post-intervention and at three-month follow-up are also presented. Kinematic results at the first and last (18^{th}) robot sessions are then presented which will be followed by the results from the qualitative component.

4.7.1 Recruitment of participants

Twenty-three participants were recruited from six NHS sites between March 2012-July 2013; 12 participants with sub-acute stroke and 11 participants with chronic stroke. The following consort flow diagram demonstrates an example of the recruitment process of participants with sub-acute stroke from one NHS site between March 2012 and July 2013 with data obtained from the NHS Trust (Figure 4.26). From this NHS site, a total of six participants with sub-acute stroke were recruited for the trial.

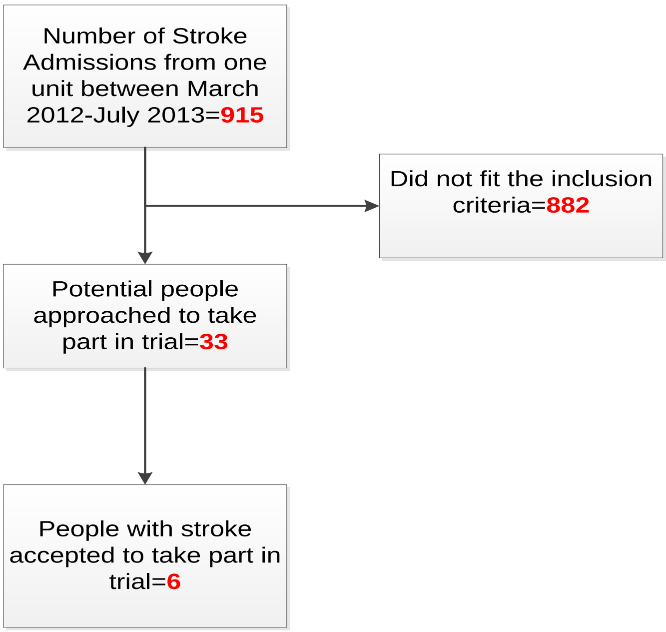


Figure 4.26 Prisma flow diagram: Recruitment of participants from one NHS Site

From all the recruitment sites, 35 participants agreed to take part, 23 participants were eligible and stratified into two groups, sub-acute and chronic. Each group was randomised into real or sham tDCS and RT. One participant from the chronic and real group dropped out of the trial and therefore 22 participants completed the trial (Figure 4.27).

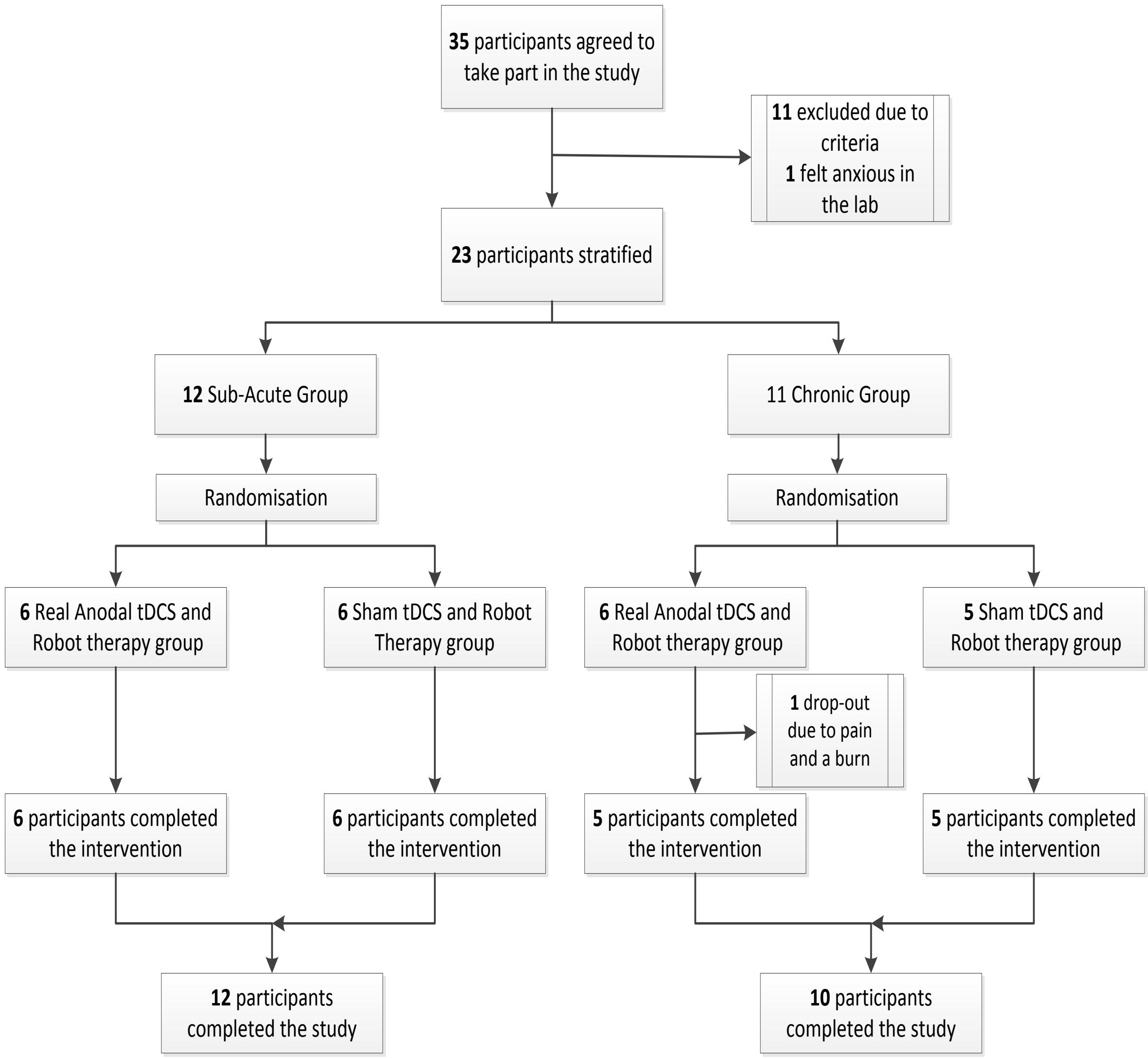


Figure 4.27 Prisma flow chart: Process of participant recruitment to completion of study

4.7.2 Screening data of participants

Twenty-five participants came to the Laboratory for the screening procedure for the trial. One participant was screened at the lab however, was taking anti-epileptic medication. Therefore, was excluded from the trial. Another participant felt anxious about the TMS equipment and decided not to take part in the study. Therefore, 23 participants completed the baseline assessment and randomised. These participants had their first diagnosed stroke, were over 18 years old, 12 were 2-16 weeks post-stroke and 11 were more than 16 weeks post-stroke. All participants had enough shoulder flexion to use the robot, good sitting balance and were able to provide informed consent. All participants scored >24 on the MMSE. The level of spasticity and also muscle strength were measured as part of the screening programme. The median and minimum/maximum scores for each measure of each sub-acute and chronic participant are presented in the Appendix. The overall median and min/max data for the MAS (shoulder extensors, internal rotators and adductors, elbow, wrist and finger flexors) and MRC measures (all muscles at the shoulder, elbow, wrist and hand joints) of both groups are presented in Table 4.2. Individual participant data can be found in Appendix H.1.

Table 4.2 Median and min/max scores of screening tests of the sub-acute and chronic groups

Measure/ Group	MAS* Median (Min/Max)	MRC** Median (Min/Max)
Sub-Acute	0 (0,2)	3.25 (2,4)
Chronic	1 (0,2)	3 (2,3)

***MAS=Modified Ashworth Scale/Score out of 5/ Median of 12 muscles tested;**
****MRC=Medical Research Council for Muscle Strength/Score out of 5/ Median of 12 muscles tested**

All participants had a median MRC score between two and four for the UL, and median level of spasticity of grade two or less (i.e. minimal spasticity and right amount of muscle power to carry out the robot trial).

Each participant also completed the TMS questionnaire to identify any contraindications (Appendix E.3.3). Four participants reported that they had tinnitus so wore ear plugs during the TMS assessments. The rest of the participants answered ‘no’ to all the TMS contraindications questions. Two participants wore hearing aids and removed this during the TMS application. None of the participants were taking any anticonvulsant medication. One participant was taking selective serotonin reuptake inhibitor medication and therefore, was excluded from the TMS assessment.

4.7.3 Demographic data of the participants

Twenty-three stroke participants were studied with a mean age of 63.4 years (SD 11.97). The mean age of the real group was 64.3 years (SD 9.96) and sham group was 62.6 years (SD 14.31). The difference in age and UL impairments between the groups receiving real and sham tDCS was non-significant (p=0.686 and 0.55 respectively). The demographic data of sub-acute and chronic participants are presented in Table 4.3 and Table 4.4 respectively. The difference between age and UL impairments was also non-significant in the sub-acute and chronic groups (p=0.121 and p=0.249 respectively).

The mean baseline FMA score of the sub-acute group was 36.7 (SD 18.4) demonstrating overall moderate UL impairment; 25% were severely impaired, 58% were moderately impaired and 17% were mildly impaired.

The mean FMA score of the chronic group was 38.36 (SD 26.75), thus, 45.5% were severely impaired, 45.5% were moderately impaired and 9.0% were mildly impaired. After four intervention sessions, CP6 dropped out of the trial due to an adverse reaction which is described in detail in section 4.7.8.

4.7.4 Concomitant treatment

Each participant continued with their standard rehabilitation sessions of physiotherapy and occupational therapy (average twice a week) during the trial and follow-up period. These sessions included UL strengthening, stretching and proprioception programmes. Two participants received a Functional Electrical Stimulation programme for the UL. More detail is presented in Table 4.5 and Table 4.6. All participants carried out a home exercise programme for their UL daily during the whole trial which was provided by their physiotherapist.

Table 4.3 Demographic data of sub-acute participants enrolled in the study

Participant Number	Site of Recruitment	Gender **(M/F)	Age (years)	Handed-Ness (L/R)***	Type of Stroke (I/H)****	FMA Baseline	Time since Stroke (months)	Location of Stroke
Sham Group								
P01	Bo[*1]	M*	52	R**	I	36	2	Right Lacunar (sub-cortical)
P02	Bo	M	71	R**	H	52	3	Right Basal Ganglia (sub-cortical)
P03	S[*2]	F*	60	R	I	59	3	Left Lacunar (sub-cortical)
P07	W[*3]	M	78	R	I	46	2	Brainstem/ lentiform nucleus/ external capsule (sub-cortical).
P09	W	F	83	R	I	49	2	Right Deep white matter/ bilateral deep attenuation (sub-cortical)
P10	Bo	F	76	R	I	39	2	Lacunar Infarct (sub-cortical)
Real Group								
P04	Bo	F	79	R	I	22	2	Left Unknown Location
P05	Ba*[4]	M	72	L	I	4	3	Right MCA***** (cortical/ Subcortical)
P06	Ly*[5]	M	68	R	I	40	2	Left Pons (sub-cortical)
P08	W	F	47	R	H	59	3	Left Basal Ganglia/Left Lateral Ventricle (sub-cortical)
P11	W	F	57	R	I	8	3	Right Internal Capsule (sub-cortical)
P12	Bo	M	63	R	I	26	2	Right internal capsule (sub-cortical)
% or Mean (SD)		**50% M 50% F**	**67.2 (11.4)**	**58% R 42% L**	**17% H 83% I**	**36.7 (18.4)**	**2.4 (0.5)**	**9% Cortical 91% Sub-Cortical**

**F/M=Female/Male ***R/L=Right/Left ****I/H= Ischaemic/Haemorrhagic *****MCA= Middle Cerebral Artery, *[1]Bo= Bournemouth, *[2]S=Southampton, *[3]W= Winchester, *[4] Ba= Basingstoke, *[5]= Lymington

Table 4.4 Demographic data of chronic participants enrolled in the study

Participant number	Site of Recruitment	Gender (M/F)*	Age (Years)	Handed-Ness **(R/L)	Type of Stroke ***(I/H)*	FMA Baseline	Time since Stroke (months)	Location of Stroke
CP2	BR*2	M	53	R	I	23	25	Right MCA territory (cortical)
CP4	W*4	M	49	R	I	17	53	Right MCA (cortical)
CP5	Bo	M	58	R	H	28	9	Left thalamus (sub-cortical),
CP7	S	M	37	R	I	37	22	Left MCA (cortical)
CP10	S	F	71	R	I	22	24	Right MCA Lentiform nucleus R Basal ganglia (Cortical/sub-cortical
Real Group								
CP1	S*1	M	68	R	I	19	35	Right MCA R carotid artery 98% block (cortical)
CP3	Bo*3	F	48	R	I	23	21	Left MCA Territory (cortical)
CP6	No*5	M	59	R	H	61	61	Right Cerebellum (sub-cortical)
CP8	Bo	M	65	R	H	32	90	Left basal ganglia (sub-cortical)
CP9	Bo	M	71	R	I	8	72	Right MCA (cortical)
CP11	BR	F	74	R	I	33	10	Left Pons (sub-cortical)
%/ Mean (SD)		**27% F 73% M**	**59.36 (11.71)**	**50% R 50% L**	**27% H 73% I**	**27.55 (13.77)**	**38.36 (26.75)**	**55% Cortical 27% Sub-Cortical 9% Cortical/ Sub-Cortical**

*** F/M=Female/Male ** R/L=Right/Left *** I/H= Ischaemic/Haemorrhagic ****MCA= Middle Cerebral Artery**

***1= Southampton *2 Bognor Regions *3 Bournemouth *4 Winchester *5 Northampton**

Table 4.5 Number of sessions and concomitant treatment received by the sub-acute group

Sub-Acute group		
Participant Number	**Number of Rehabilitation Sessions (per week)**	**Type of Intervention**
P01	Physiotherapy/Occupational Therapy sessions twice a week	UL Stretching and Strengthening programme FES and reaching with UL
P02	Physiotherapy session once a week	UL Strengthening Exercises
P03	Physiotherapy session once every two weeks	Hand Strengthening Exercises
P04	Physiotherapy/Occupational Therapy sessions twice a week	UL Strengthening Exercises
P05	Physiotherapy session once a week	UL Active Assisted Movements UL Stretching programme
P06	Daily	Home UL exercise programme
P07	Daily	Home UL exercise programme
P08	Physiotherapy session once a week	UL strengthening exercise and coordination programme
P09	Daily	Home UL exercise programme
P10	Physiotherapy/occupational therapy session once a week	UL strengthening exercise programme and retraining of activities of daily living
P11	Daily	Home strengthening UL programme
P12	Physiotherapy session once a week	UL stretching and functional activities programme
	Daily	Home UL strengthening programme

Table 4.6 Number of sessions and concomitant treatment received by the chronic group

Chronic Group		
CP1	Physiotherapy session and exercise class twice a week	UL stretching programme Functional task two handed practice
CP2	Daily	Home UL exercise programme and Gym once a week
CP3	Daily	Home Exercise Programme
	Once a week	Gym
CP4	Daily	Home Exercise Programme
	Once a week	Gym
CP5	Physiotherapy sessions twice a week	Stretching and strengthening UL programme Functional repetitions of UL movements Functional Electrical Stimulation of the shoulder muscles
CP6	Daily	UL Home Exercise Programme
	Once a week	Gym
CP7	Daily	Home Exercise Programme
	Once a week	Aqua gym
CP8	Physiotherapy session once a week	Stretching and strengthening UL programme
CP9	Daily	UL stretches
	Physiotherapy session twice a week	UL exercise programme
CP10	Daily	UL Home Exercise Programme
	Physiotherapy session once every three weeks	UL stretching programme

4.7.5 Main clinical findings

For the sub-acute group, significant improvements in FMA, ARAT, MAL and SIS at post-intervention and follow-up of the sub-acute group were found. No significant differences were found in MTS and HAD. No significant differences were found between the real and sham groups for all outcome measures except MAL which showed a significant improvement in the sham group compared to the real group at post-intervention.

For the chronic group, significant improvement in FMA was found at post-intervention and follow-up for the whole group. No significant improvements in ARAT, MAL or HAD and between the real and sham groups were found.

Significant improvements were found in SIS and significant increase in MTS at three-month follow-up.

This section presents these results of the clinical measures: FMA, ARAT, MTS, MAL, SIS and HAD. Twenty-two participants completed all the clinical measures except the HAD at the three assessment time-points. This outcome measure was introduced late in the study, and so only 20 participants completed it.

4.7.5.1 Results of FMA

Statistical analysis was described on Page 128. The data for FMA were normally distributed and therefore, parametric statistics were used. The data were first analysed from the whole sample and then put into the regression model to compare factors such as tDCS versus sham groups. For the whole sample, repeated measures ANOVA were applied to the FMA scores.

Mauchly's test of sphericity was significant and therefore, Greenhouse-Geisser test was used. Significant differences ($p=\leq 0.001$) were found for the three time points of the whole sample. Using paired-samples t-test for post-hoc analysis showed a significant difference between the baseline and post-intervention scores ($p=0.001$) and the baseline and the three-month follow-up scores ($p=0.000$) of the sub-acute group (Table 4.7) (Appendix H.2.1). Significant improvements were also found at post-intervention but not at follow-up for the chronic group ($p=0.01$ and $p=0.1$ respectively). At baseline the mean score of the sub-acute group was 36.67 (SD 18.36), and the mean change from baseline to post-intervention +10.25 (15.53%). The mean change from baseline to follow-up was +10.58 (16.03%) (Table 4.7). At baseline the mean score of the chronic group was 24.20 (SD 8.60), and the mean change from baseline to post-intervention +5.80 (8.78%). The mean change from baseline to follow-up was +3.00 (4.55%) (Table 4.7).

Table 4.7 Mean FMA scores at baseline, post-intervention and follow-up of the real and sham groups of sub-acute and chronic groups

	Baseline	Post-interven-tion	Follow-up	Change[*2]	p-value[*4]	Change	p-value[*4]
	(B)	(P)	(F)	(P-B) (%)	(P-B)	(F-B) (%)	(F-B)
Sub-acute group							
Overall Mean (SD)*3	36.67 (18.36)	46.92 (17.78)	47.3 (18.00)	+ 10.25 (15.53%)	0.000*	+10.58 (16.03%)	0.001*
Real Group Mean (SD)	26.50 (20.53)	37.00 (19.40)	38.33 (18.95)	+10.50 (15.90%)	0.002*	+11.83 (17.92%)	0.014*
Sham Group Mean (SD)	46.83 (8.47)	56.83 (9.13)	56.00 (13.13)	+10.00 (15.15%)	0.001*	+9.33 (14.14%)	0.035*
Chronic group							
Overall Mean (SD)*3	24.20 (8.60)	30.00 (10.23)	27.20 (11.01)	+5.80 (8.78%)	0.01*	+3.00 (4.55%)	0.092
Real Group Mean (SD)	23.00 (10.27)	29.60 (12.34)	24.60 (10.76)	+6.60 (10.00%)	0.045*	+1.60 (2.42%)	0.195
Sham Group Mean (SD)	25.40 (7.57)	30.40 (9.10)	29.80 (11.84)	+5.00 (7.58%)	0.028*	+4.40 (6.67%)	0.224
Whole sample significance level[*4]				p=0.000*4		p= 0.000*4	

[*1]FMA= Fugl-Meyer Assessment/ Maximum Score is 66, [*2] Change=% from the Maximum Score, [*3]SD= Standard Deviation, [*4] Paired-Samples t-test, (*) significant at p=≤0.05

When linear regression was applied to the FMA post-intervention scores, two significant predictors were found: (a) FMA baseline score (p=0.000) and (b) cortical versus sub-cortical stroke factor was (p=0.034) at a regression value of 5.814 (Table 4.8). This means that the effect of having a sub-cortical stroke as opposed to a cortical stroke increased the expected post-intervention FMA score for the whole sample by 5.8 points. The scores of each FMA score of the participants with cortical and sub-cortical strokes are presented in Figure 4.29. When repeated measures ANOVA was applied FMA data of the sub-cortical and cortical groups at the three-time points, significant differences were found (p=≤0.001) for the sub-cortical group however, non-significant for the cortical group (p=0.471).

Table 4.8 Linear regression statistics of FMA post-intervention scores

Regression Model	B*2	Standard Error	Significance
FMA Baseline	1.005	0.115	0.000*1
FMA Baseline x Real/Sham	-0.140	0.125	0.280
Time since Stroke	-0.012	0.041	0.777
Real vs sham groups	4.703	4.509	0.313
Cortical vs subcortical strokes	5.814	2.485	0.034*1
Real/sham vs cortical/sub-cortical	1.335	4.823	0.786

***1= Significant, *2= Regression Value**

However, the interaction of real or sham with cortical and sub-cortical strokes was not significant. The regression value of the real versus sham tDCS intervention was 4.703 however, this was non-significant. This implies that being in the real tDCS group increased the expected post-intervention FMA score by 4.7 points. However, the value had a high standard error of 4.509 which means that a larger sample was needed in order to obtain a significant value. Other factors, such as time since stroke, did not have an influence on the post-intervention scores.

Table 4.9 Linear regression statistics of FMA follow-up scores

Regression Model	B*2	Standard Error	Significance
FMA Baseline	0.919	0.299	0.000*1
FMA Baseline x Real/Sham	-0.189	0.218	0.399
Time since Stroke	-0.067	0.072	0.366
Real vs sham groups	4.875	7.878	0.545
Cortical vs subcortical strokes	9.385	4.343	0.047*1
Real/sham vs cortical/sub-cortical	7.705	8.491	0.379

***1= Significant, *2= Regression Value**

When linear regression was applied to the FMA three-month scores, a similar result was obtained (Table 4.9). The baseline and the cortical/sub-cortical factors were significant on the three-month follow-up scores ($p=\leq 0.001$) and (p=0.047) respectively. A higher regression value was found for the cortical/sub-cortical factor implying that the effect of having a sub-cortical stroke as opposed to a cortical stroke increased the expected follow-up score by 9.385. However, the interaction with real or sham groups with cortical or sub-cortical strokes was non-significant.

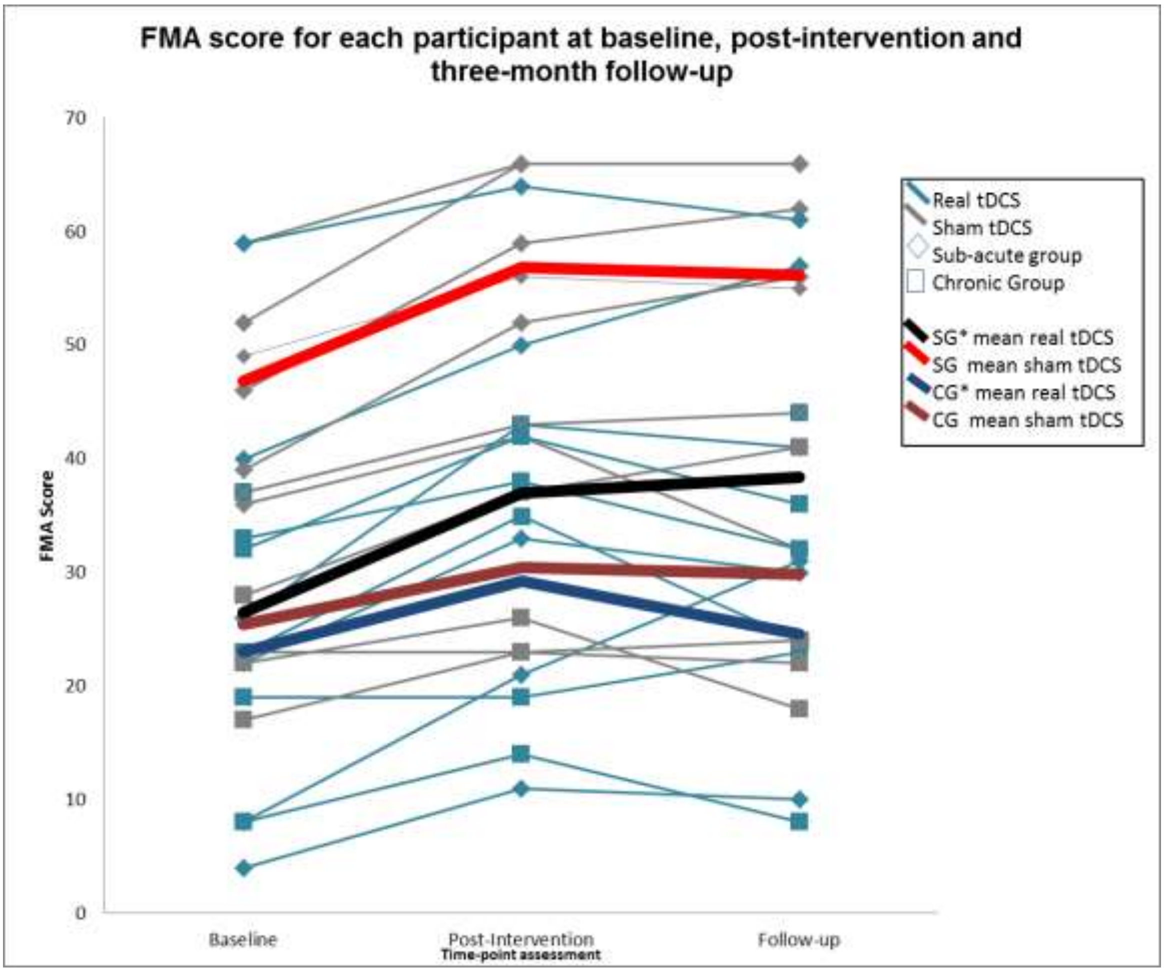


Figure 4.28 Individual participant FMA scores and means of sub-acute (real and sham) and chronic groups (real and sham) at baseline, post-intervention and follow-up

(*SG= Sub-acute group and CG= Chronic Group)

Each individual FMA data at the baseline, post-intervention and follow-up is presented in Figure 4.28. From the graph it is noted that twenty participants improved UL impairments. It is noted that the real and sham groups show a very similar pattern at the three time-points. Twenty participants showed an improvement in the FMA score at post-intervention but this improvement tended to minimally decrease at three-month follow-up. However, the final score was always higher than the baseline score. From Figure 4.28, it is noted that the participants in the sub-acute group receiving sham stimulation had a higher baseline FMA score than the participants in the real group. The difference in FMA data at the three time-points between the sub-cortical and cortical groups are displayed in Figure 4.29. It is noticed that the participants with a sub-cortical stroke had a higher baseline FMA score than the participants with a cortical stroke. There was a clear indication that participants with sub-cortical stroke showed a greater UL improvement at post-intervention. Participants with a sub-cortical stroke had a higher baseline FMA score than the participants with a cortical stroke.

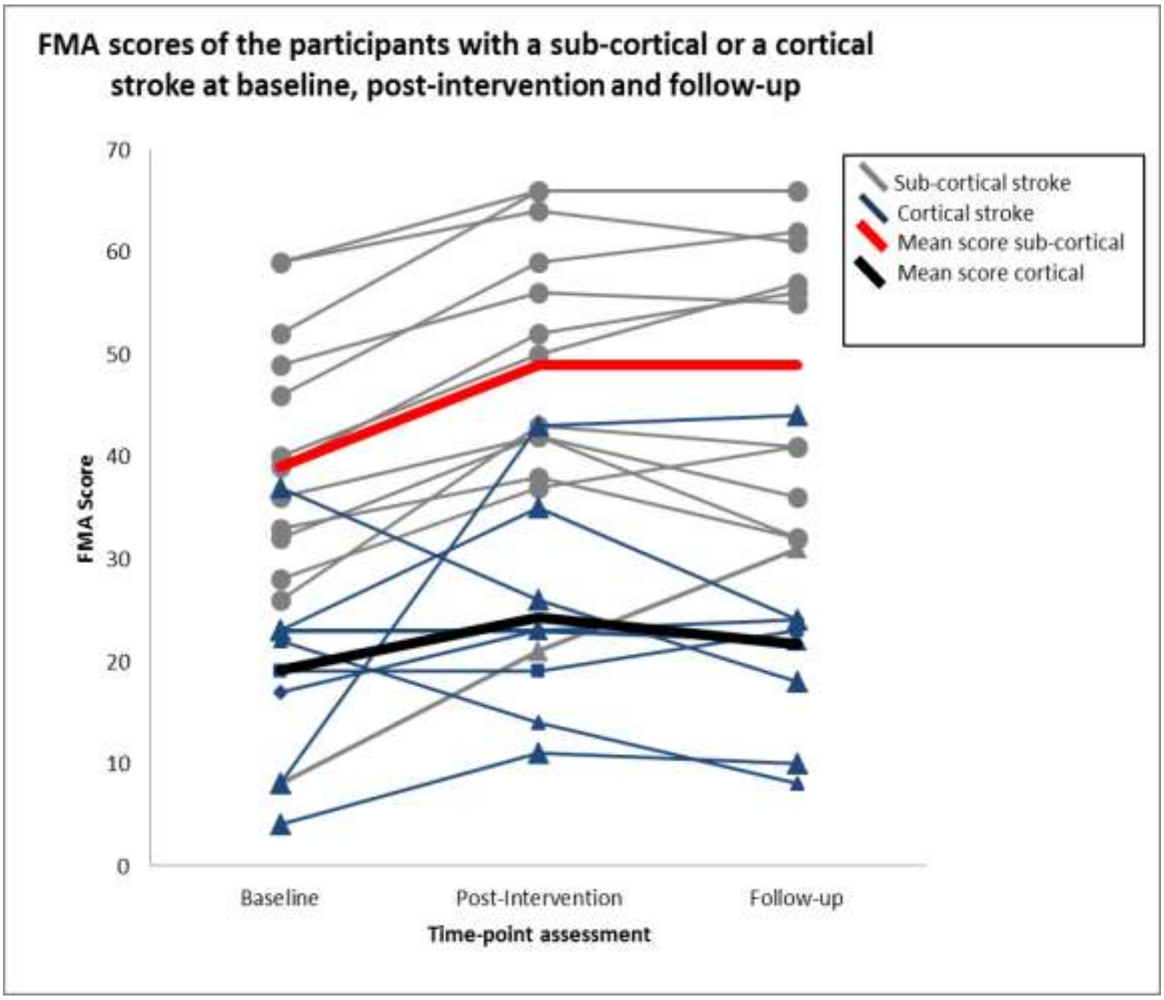


Figure 4.29 Individual participant FMA scores and means of the participants who had a sub-cortical or a cortical stroke at baseline, post-intervention and follow-up

4.7.5.2 Results of ARAT

The data were first analysed from the whole sample and then put into the regression model. The ARAT data was not normally distributed and therefore nonparametric tests were used. Friedman’s ANOVA was applied to test the overall effect of the intervention and the three time-points and a significant difference was found (p=≤0.001) (Appendix H.2.2). Post-hoc analysis using the Wilcoxon Signed Rank test was carried out to compare the baseline with the post-intervention scores and a significant value (p=0.001) was found. Also a significant value was found between the baseline with the three-month scores (p=0.004) (Table 4.10) (Appendix H.2.2).

Table 4.10 Median ARAT scores at baseline, post-intervention and follow-up of the real and sham groups of sub-acute and chronic groups

	Baseline	Post-interven-tion	Follow-up	Change *[2]	p-value[*3]	Change*[2]	p-value[*3]
	(B)	(P)	(F)	(P-B) (%)	P-B	(F-B) (%)	F-B
Sub-acute group							
Overall median (min,max)	33.50 (0,56)	48.50 (0,57)	50.00 (0,57)	+15.00 (26.32%)	0.03*	+16.50 (28.95%)	0.05*
Real group Median (min,max)	11.50 (0,50)	21.00 (0,57)	23.50 (0,57)	+9.50 (16.67%)	0.042*	+12.00 (21.05%)	0.042*
Sham groupMedian (min,max)	39 .00 (6,65)	54.00 (29,56)	53.50 (30,57)	+15.00 (26.32%)	0.043*	+14.50 (25.44%)	0.028*
Chronic group							
Overall Median (min,max)	6.00 (0,16)	8.00 (0,18)	8.00 (0,13)	+2.00 (3.51%)	0.176	+2.00 (3.51%)	0.796
Real group Median (min,max)	4.00 (0,17)	8.00 (0,18)	7.00 (0,13)	+4.00 (7.02%)	0.414	+3.00 (5.26%)	0.581
Sham Group Median (min,max)	7.00 (3,11)	8.00 (3,14)	8.00 (3,13)	+1.00 (1.75%)	0.180	+1.00 (1.75%)	0.083
Whole Sample overall significance level				p= 0.001*[3]		p= 0.004*[3]	

[*1] Action Research Arm Test/Maximum Score is 57, [*2] Change=% from the Maximum Score, [*3] Wilcoxon-Signed Rank Test, (*) Significant at p=≤0.05

At baseline the median score of the sub-acute group was 33.50 (min 0, max 56), and the mean change from baseline to post-intervention was +9.00 (15.5%). The mean change from baseline to follow-up was +11.5 (20.0%). At baseline the mean score of the chronic group was 6.0 (min 0, max 18) and the mean change from baseline to post-intervention +2.0 (3.51%). The mean change from baseline to follow-up was +2 (4.00%). Significant differences were found at post-intervention and follow-up for the sub-acute but not for the chronic group. When the linear regression model was applied to the ARAT post-intervention scores, the factor of cortical and sub-cortical strokes did not reach significance (

Table 4.11). A negative B value of 4.754 for the real versus sham factor was found, indicating that being in the sham group increased the post-intervention ARAT score by 4.754 as opposed to being in the real group. However, this also did not reach significance level. A significant finding was found however for the baseline score (p=≤0.001) which implies that the baseline score does influence the post-intervention score.

Table 4.11 Linear regression statistics of ARAT post-intervention scores

Regression Model	B*2	Standard Error	Significance
ARAT Baseline	0.894	0.122	0.000*1
ARAT Baseline x Real/Sham	0.111	0.173	0.532
Time since Stroke	-0.068	0.069	0.342
Real vs sham groups	-4.754	4.355	0.292
Cortical vs subcortical strokes	9.385	4.166	0.128*1

***1= Significant, *2= Regression Value**

For the three-month follow-up ARAT scores, a similar result was found (Table 4.12).

Table 4.12 Linear regression statistics of ARAT follow-up scores

Regression Model	B*2	Standard Error	Significance
ARAT Baseline	0.914	0.149	0.000*1
ARAT Baseline x Real/Sham	0.178	0.211	0.412
Time since Stroke	-0.106	0.085	0.229
Real vs sham groups	-5.483	5.316	0.319
Cortical vs subcortical strokes	4.194	5.086	0.422*1

***1= Significant, *2= Regression Value**

The ARAT scores of each participant at baseline, post-intervention and follow-up is presented in Figure 4.30. It is noted that the sub-acute participants showed a greater improvement in UL function and dexterity in relation to the baseline than the chronic group.

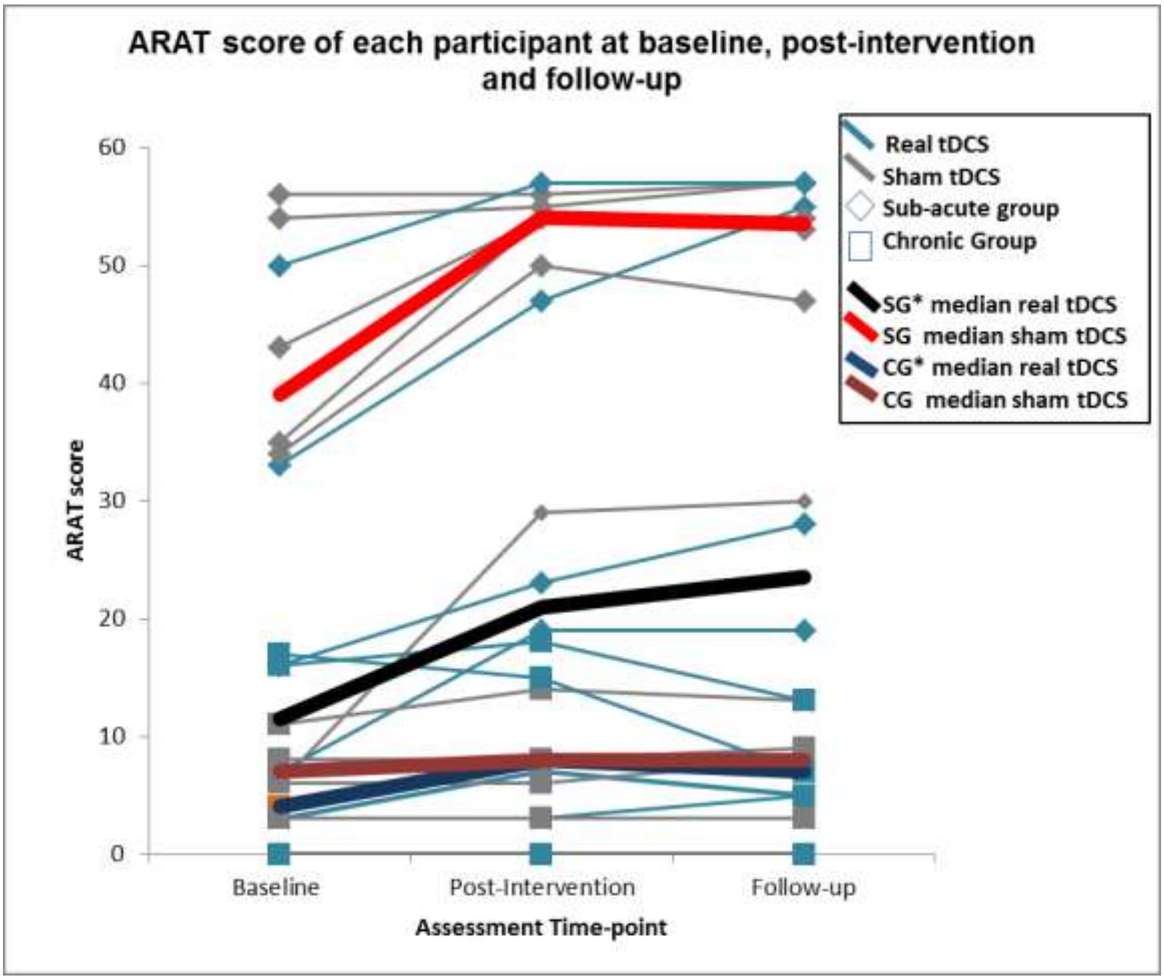


Figure 4.30 Individual participant ARAT scores and medians of the sub-acute (real and sham) and chronic groups (real and sham) at baseline, post-intervention and follow-up

(*SG= Sub-acute group and CG= Chronic Group)

It is also noted that participants in the real group showed a similar improvement to participants in the sham group at post-intervention. At three-month follow-up, the scores tended to slightly improve or remain the same in both the real and sham groups (Figure 4.30).

4.7.5.3 Results of MTS

The data were first analysed for the whole sample and then put into the regression model. The data for quality of movement were not normally distributed and therefore, nonparametric tests were used. The data for angle of catch were normally distributed and therefore parametric tests were used. Non-significant differences at the three time points and between the real and sham groups were found (Appendix H.2.3).

At baseline, the median score of the quality of movement of the elbow and wrist flexors was 1.00 (min 0, max 2) and the median change from baseline to post-intervention and follow-up was -1.00 (20.00%) for the sub-acute group (Table 4.13). At baseline, the median score of the quality of movement of the elbow flexors at baseline was 1.00 (min 1, max 3) and the median change from baseline to post-intervention and follow-up was 0 (0%) for the chronic group. For the wrist flexors, the median score of quality of movement at baseline was 2.00 (min 0, max 3) and the median change from baseline to post-intervention was 0 (0%) and from baseline to follow-up was -1.00 (20.00%) (Table 4.13). The results of the quality of movement and angle of catch sub-section of the measure of each participant are presented in the Appendix H.2.3.

Table 4.13 Median MTS[*1] quality of movement scores at baseline, post-intervention of sub-acute and chronic groups

	Baseline	Post-Interven-tion	Follow-Up	Change*2	p-value*3	Change*2	p-value*3
	(B)	(P)	(F)	(P-B) (%)		(F-B) (%)	
Sub-acute group							
Elbow Flexors Median (min, max)	1.00 (0,2)	0 (0,2)	0 (0,2)	-1.00 (20.00%)	0.655	-1.00 (20.00%)	0.705
Wrist Flexors Median (min, max)	1.00 (0,2)	0 (0,2)	0 (0,2)	-1.00 (20.00%)	0.655	-1.00 (20.00%)	1.00
Chronic Group							
Elbow Flexors Median (min, max)	1.00 (1,3)	1.00 (0,3)	1.00 (1,2)	0 (0%)	0.705	0 (0%)	0.083
Wrist Flexors Median (min, max)	2.00 (0,3)	2.00 (0,3)	1.00 (0,2)	0 (0%)	0.516	-1 (20.00%	0.577
Whole sample overall significance level				Elbow Flexors p= 0.100*3		Elbow Flexors p= 0.206*3	
				Wrist Flexors p=0.776*3		Wrist Flexors p=0.627*3	

***1 MTS= Modified Tardieu Scale/ Score 0-5 grade of the muscles reaction where a score of 0 represented no resistance during movement and a score of 5 represents full resistance during slow movement of the elbow and wrist flexors. *2= Change from maximum score (5 points), *3= Wilcoxon-Signed Rank Test**

At baseline, the mean score of the angle of catch of the elbow flexors at baseline was 47.6° (SD 40.3) and the mean change from baseline to post-intervention was +4.81° (3.32%) and from baseline to follow-up was +12.3° (8.48%) for the sub-acute group. An increase in angle of catch indicates a decrease in spasticity. For the wrist flexors, the median score of quality of movement at baseline was 25.00 (SD 17.5), the median change from baseline to post-intervention was +8.70 (12.43%) and from baseline to follow-up was +4.90 (7.00%) (Table 4.14).

Table 4.14 Mean MTS[*1] angles of catch at baseline, post-intervention and follow-up of sub-acute and chronic groups

	Baseline (°)	Post-Interven-tion (°)	Follow-Up (°)	Change *2 (°)	p-value*4	Change *2 (°)	p-value*4
	(B)	(P)	(F)	(P-B) (%)	(P-B)	(F-B) (%)	(F-B)
Sub-acute group							
Elbow Flexors Mean (SD)*3	47.5 (40.3)	49.0 (30.7)	61.8 (35.2)	+4.81 (3.32%)	0.153	+12.3 (8.48%)	0.108
Wrist Flexors Mean (SD)	25.00 (17.5)	31.0 (10.0)	33.8 (16.4)	+8.70 (12.43%)	0.742	+4.90 (7.00%)	0.317
Chronic Group							
Elbow Flexors Mean (SD)	42.10 (36.10)	65.2 (33.00)	71.90 (37.80)	19.10 (13.17%)	0.898	17.00 (11.72%)	0.872
Wrist Flexors Mean (SD)	15.60 (12.70)	27.30 (5.50)	23.50 (19.30)	5.70 (8.14%)	0.061	0.10 (0.14%)	0.029*
Whole sample overall significance level				Elbow Flexors p= 0.583*4		Elbow Flexors p=0.694*4	
				Wrist Flexors p=0.451*4		Wrist Flexors p=0.410*4	

[*1] MTS= Modified Tardieu Scale/ Score 0-5 grade of the muscles reaction where a score of 0 represented no resistance during movement and a score of 5 represents full resistance during slow movement of the elbow and wrist flexors. [*2]= Change from maximum score: Elbow flexion (145°) and Wrist Flexion (70°), [*3] SD= Standard Deviation, [*4]= Paired samples t-test, (*)= Significant at p=≤0.05

At baseline, the mean score of the angle of catch of the elbow flexors was 42.10° (SD 36.10), the mean change from baseline to post-intervention was +19.10° (13.17%) and from baseline to follow-up was +17.00° (11.72%) for the chronic group. For the wrist flexors, the median score of quality of movement at baseline was 15.60 (SD 12.70), the median change from baseline to post-intervention was +5.70 (8.14%) and from baseline to follow-up was +0.10 (0.14%) (Table 4.14). When Paired-Samples t-test was applied to the chronic and sub-acute groups, a significant increase in angle of catch at the wrist flexors of the chronic group at three-month follow-up was found.

4.7.5.4 Results of MAL

The data were first analysed for the whole sample and then put into the regression model. The data were not normally distributed and therefore nonparametric statistics were used.

A significant difference was found at the three time points for all the participants (p=0.002) when Friedman's ANOVA was applied (Appendix H.2.4). When post-hoc analysis was carried out significant differences was found between the baseline and post-intervention and three-month intervention time points (p=0.006) and (p=0.002) respectively of the sub-acute group (Table 4.15). At baseline, the mean score of MAL was 1.33 (SD 1.27) and the mean change from baseline to post-intervention was +0.97 (19.40%) and follow-up was 1.25 (25.00%) for the sub-acute group. For the chronic group, at baseline the median score of MAL was 0.46 (SD 0.50) and the mean change from baseline to post-intervention was +0.03 (0.60%) and follow-up was 0.13 (2.60%) for the chronic group (Table 4.15). The 'quality of movement' section of the MAL data at baseline, post-intervention and follow-up scores of each participant are presented in the Appendix H.2.4. When linear regression was applied to the post-intervention and follow-up data, there were no significant differences between all the factors within the model including the real and sham groups.

Table 4.15 Mean MAL*1 scores at baseline, post-intervention and follow-up of the real and sham groups of sub-acute and chronic groups

	Baseline	Post-Interven-tion	Follow-Up	Change*2	p-value*4	Change*2	p-value*4
	(B)	(P)	(F)	(P-B) (%)	(P-B)	(F-B) (%)	(F-B)
Sub-acute group							
Overall Mean (SD)*3	1.33 (1.27)	2.30 (1.76)	2.58 (1.80)	+0.97 (19.40%)	0.006*	1.25 (25.00%)	0.002*
Real Group Mean (SD)	1.30 (1.47)	1.82 (2.78)	2.17 (2.07)	+0.52 (10.40%)	0.116	0.87 (17.40%)	0.028*
Sham Group Mean (SD)	1.36 (1.18)	2.78 (1.65)	2.99 (1.57)	+1.42 (0.28%)	0.027*	1.63 (32.60%)	0.028*
Chronic group							
Overall Mean (SD)*3	0.46 (0.50)	0.49 (0.74)	0.59 (0.81)	+0.03 (0.60%)	0.672	0.13 (2.60%)	0.484
Real Group Mean (SD)	0.49 (0.60)	0.49 (0.66)	0.69 (0.72)	0.00 (0.00%)	0.854	0.20 (4.00%)	0.144
Sham Group Mean (SD)	0.42 (0.44)	0.48 (0.90)	0.50 (0.97)	+0.06 (1.20%)	1.000	0.08 (1.60%)	0.715
Whole sample overall significance level				0.015*4		0.001*4	

***1 Motor Activity Log-28 (Quality of Movement Section), *2 Change=% from the Maximum Score (5 points), *3 SD= Standard Deviation, *4 *Wilcoxon-Signed Rank Test= Significant at p=≤0.05**

4.7.5.5 Results of SIS

The results for each domain of the SIS at the time-points of each participant are presented in the Appendix H.2.5. A higher score referred to a decrease in impact of the stroke on the person. It was noted that there was a decreased stroke impact at post-intervention to the baseline scores in all domains for all the participants. All domains improved in the sub-acute group. In the chronic group, mean scores were increased in strength, memory, mobility, hand function, social participation domains at post-intervention but a small decrease was noted in the emotion, communication, ADLs, and perceived stroke recovery. However, at follow-up, mean scores increased in all domains. The representation of the SIS domains at the three time-points in presented in Figure 4.31.

It was noticed that both the real and sham sub-acute group showed significant improvement at post-intervention (p=0.001 real and p=0.094 sham) from baseline. These improvements were maintained and therefore at three-month follow-up significant improvements were also found in the real and sham groups (p=≤0.001 real and p=0.006 sham). The chronic group did not show any significant improvements at post-intervention however, they showed significant improvements at follow-up (p=0.031 real and p=0.035) (Table 4.16).

Table 4.16 SIS domains of all participants at the three time-points-up of the real and sham groups of sub-acute and chronic groups

	Baseline	Post-Interven-tion	Follow-Up	Change*2	p-value*4	Change*2	p-value*4
	(B)	(P)	(F)	(P-B)	(P-B)	(F-B)	(F-B)
Sub-acute group							
Overall Mean (SD)*3	57.97 (21.80)	75.02 (15.65)	73.29 (14.74)	+17.05	0.01*	+15.32	0.000*
Real Group Mean (SD)	54.99 (18.25)	68.88 (18.60)	62.50 (55.00)	+13.89	0.001*	+7.51	0.000*
Sham Group Mean (SD)	55.43 (17.80)	73.89 (17.68)	76.05 (17.18)	+18.46	0.094	+20.62	0.006*
Chronic Group							
Overall Mean (SD)*3	58.12 (26.51)	58.51 (23.35)	61.66 (24.93)	+0.39	0.168	+3.54	0.005*
Real Group Mean (SD)	55.94 (12.93)	58.14 (13.53)	59.67 (15.19)	+2.20	0.295	+3.73	0.031*
Sham Group Mean (SD)	57.48 (13.00)	59.02 (18.51)	62.11 (17.44)	+1.54	0.502	+4.63	0.035*
Whole sample overall significance level				p=0.000*4		p=0.000*4	

***1 Stroke Impact Scale *2 Change=% from the Maximum Score (100 points), *3 SD= Standard Deviation, *4= Paired Samples t-test-Significant at p=≤0.05**

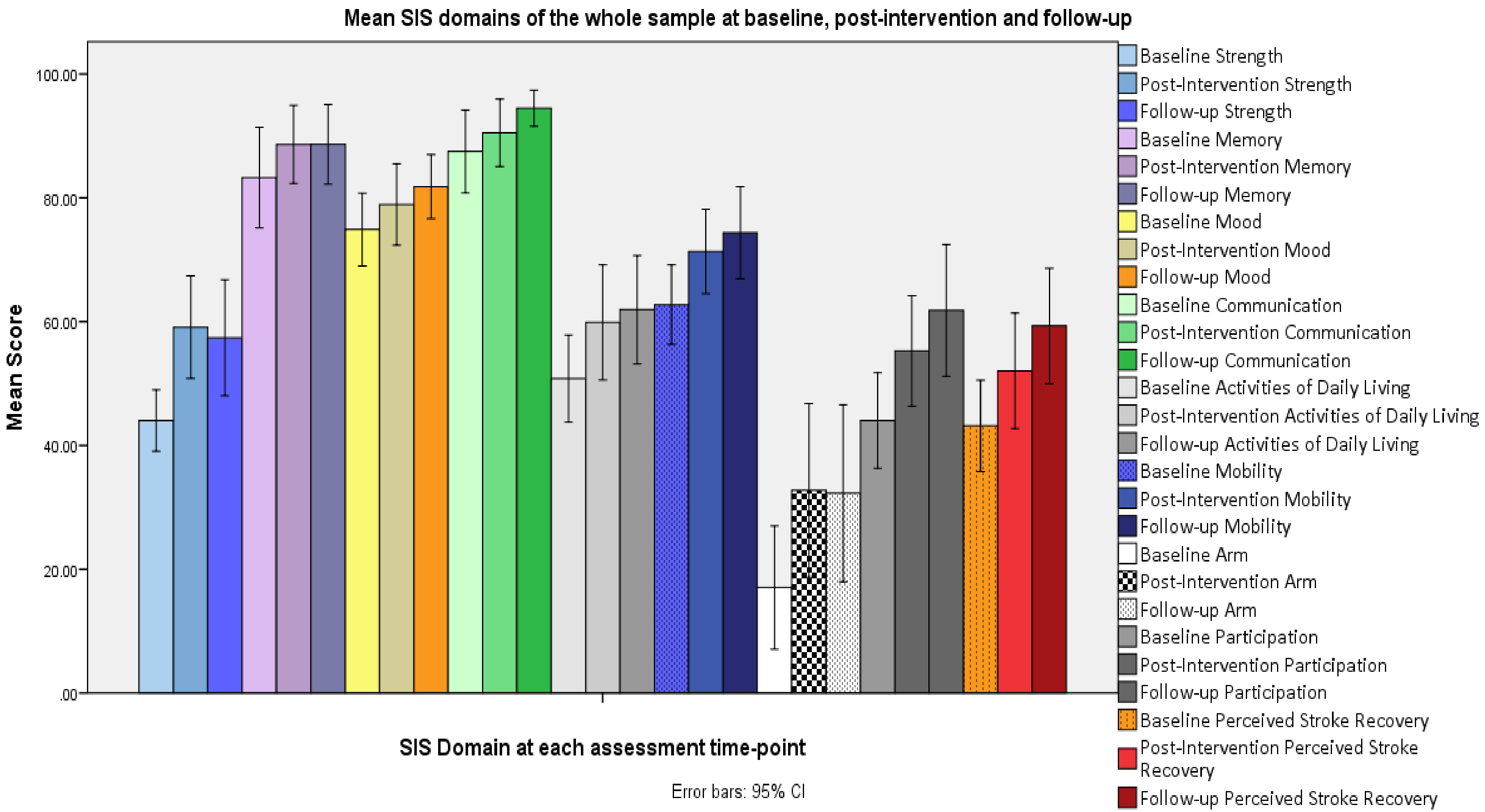


Figure 4.31 SIS domains of all participants at the three time-points-up of the real and sham groups of sub-acute and chronic groups

The participation and strength domains were chosen for further data analysis. The mean value of the participation and strength domains at baseline was +39.32% (SD 18.72) and +45.31% (SD 11.65) respectively for the sub-acute group. The change from post-intervention from the baseline score was +13.82% for participation and +20.84% for strength for the sub-acute group. The change from the follow-up score to the baseline score was +24.50% for participation and +22.92% for strength.

For the chronic group, the mean value of the participation and strength domains at baseline was 49.69% (SD 14.62) and 42.50% (SD 10.94) respectively. The change from post-intervention from the baseline score was +8.12% for participation and +8.13% for strength. The change from the follow-up score to the baseline score was +9.69% for participation and +1.88% for strength.

Repeated measures ANOVA (Sphericity assumed test) were applied to the data for the whole sample and significant differences were found for participation ($p=\leq0.001$) and strength ($p=0.003$) domains at the three points. Post-hoc analysis showed a significant difference between the post-intervention and baseline scores for participation ($p=0.009$) and strength ($p=0.01$) and between the three-month follow-up and baseline scores for participation ($p=\leq0.001$) and strength ($p=0.015$) of the participation domain. When the data was applied to the linear regression model non-significant differences were found in participation and strength between the real and sham group, cortical and sub-cortical groups.

4.7.5.6 Results of HAD

Twenty participants completed the HAD at baseline, post-intervention and at follow-up. The data was not normally distributed and therefore, nonparametric tests were used.

Baseline median scores of the anxiety and depression sections was 3 (SD min 1, max 11) and 2.5 (min 0, max 12) respectively for the sub-acute group. No change in was noted at post-intervention. At follow-up, a very small decrease of -0.5 (2.38%) was noted in the anxiety section from the baseline value. The baseline median score was slightly higher for the depression section 7 (min 2, max 10) for the chronic group. The baseline median score for the anxiety section was 3.5 (min 0, max 13). A small change of +1.00 (+4.76%) was noted in anxiety at post-intervention from baseline. The depression score increased by +0.50 (+2.38%) at post-intervention from the baseline score. At follow-up the change from the baseline score in anxiety was +0.50 (+2.38%) and for depression was -0.50 (-2.38%). The data of each participant at the three time-points can be found in the Appendix H.2.6. All these changes did not reach a level of significance.

4.7.6 Main neurophysiological findings

The RMT and MEP recruitment curves of the anterior deltoid and extensor digitorum muscle were measured for all participants at baseline, post-intervention and three-month follow-up. The active motor threshold was only recorded for the first participant. This procedure was very tiring for the participants and therefore, it was decided that this measurement would not be included in the assessments for the rest of the participants.

After data analysis was carried out at the TMS Laboratory at the Institute of Neurology, problems were identified with the data. It was noticed that in several participants MEPs were not elicited even at high intensities. Data analysis of the RMT and MEP amplitude was only possible for the extensor digitorum muscle of five sub-acute participants.

4.7.6.1 Results of RMT

The RMT and MEP amplitude (at 100% RMT) of the extensor digitorum muscle of five sub-acute participants was analysed and is presented in Table 4.17 and Table 4.18. A decrease in RMT depicts an increase in cortico-spinal excitability.

Table 4.17 Resting Motor Threshold of the extensor digitorum muscle at baseline, post-intervention and follow-up

Participant	RMT*[1] at the Extensor Digitorum Muscle (%)				
	Baseline (B)	Post-Intervention (P)	Follow-Up	Change (B-P)	Change (F-B)
P02	50	70	N/E	+20	-
P03	50	N/E*[2]	54	-	+4
P06	65	65	65	0	0
P07	86	N/E	72	-	-14
P11	88	N/E	74	-	-14

***1 RMT= Resting Motor Threshold**

***2N/E= Not Elicited**

It is noted that most participants needed a very high intensity in order to elicit a MEP at the extensor digitorum muscle. Two participants had a decreased RMT at follow-up and two participants had an increased RMT at follow-up.

Table 4.18 MEP amplitude of the extensor digitorum muscle at baseline, post-intervention and follow-up

Participant	MEP Amplitude (μV) at RMT*[1] of the Extensor Digitorum Muscle (%)				
	Baseline (B)	Post-Intervention (P)	Follow-Up	Change (B-P)	Change (F-B)
P02	69.23	126.69		+ 57.46	-
P03	89.79		56.11	-	-33.68
P06	59.19	130.53	62.75	+71.34	+3.56
P07	57.68	-	57.71	-	+0.03
P11	73.97		56.51	-	-17.46

***1RMT=Resting Motor Threshold/Score out of 100**

Although, the data presented is minimal, it is noted MEP amplitude increased in P02 (sham stimulation) and in P06 (real tDCS) at post-intervention. At follow-up, P03 and P11 had a decreased MEP amplitude and P06 and P07 had increased MEP amplitudes.

4.7.6.2 MEP recruitment curves of the extensor digitorum muscle at baseline post-intervention and at follow-up

Two recruitments curves of P02 (received sham stimulation) and P06 (received real stimulation) were analysed. From the P02 curves it is noted that the baseline and post-intervention curves are very similar in shape and a slight increase in MEP amplitude is noted at 110% of RMT at post-intervention (Figure 4.32). From P06's recruitment curve, an increase in MEP amplitude at 100% at post-intervention and at follow-up was found (Figure 4.33).

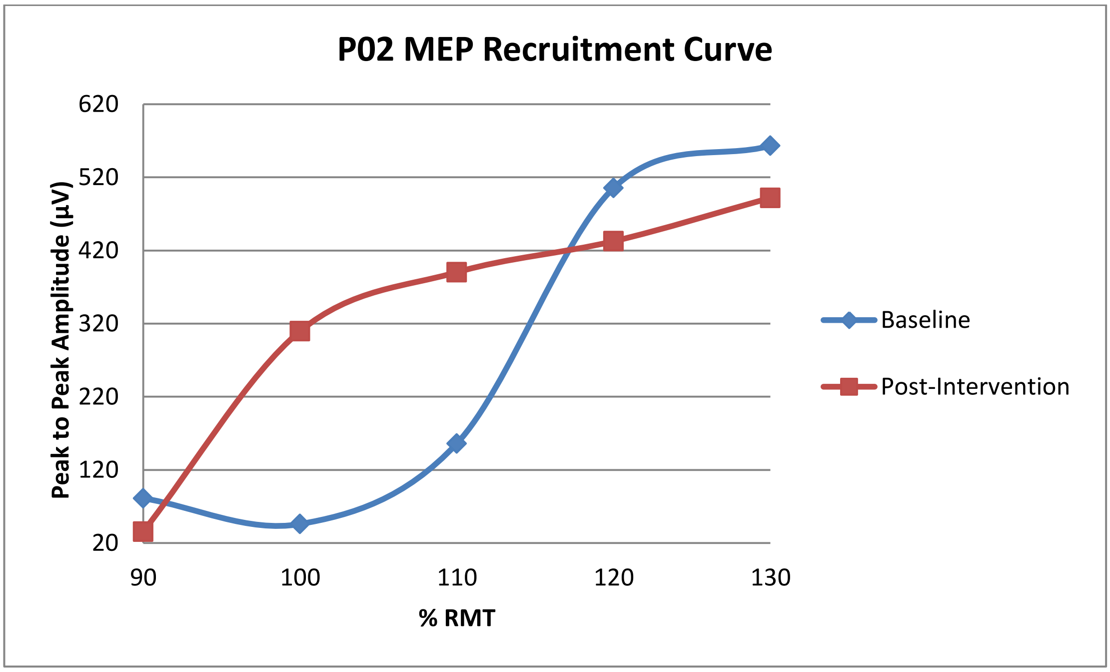


Figure 4.32 MEP recruitment curve of the extensor digitorum muscle at baseline and post-intervention of P02

In summary, the extensor digitorum MEPs were elicited in 5 participants with sub-acute stroke. It is noted that high RMT's was needed to elicit 50(µV) MEPs. In two participants, an increase in MEP amplitude was noted at RMT at post-intervention.

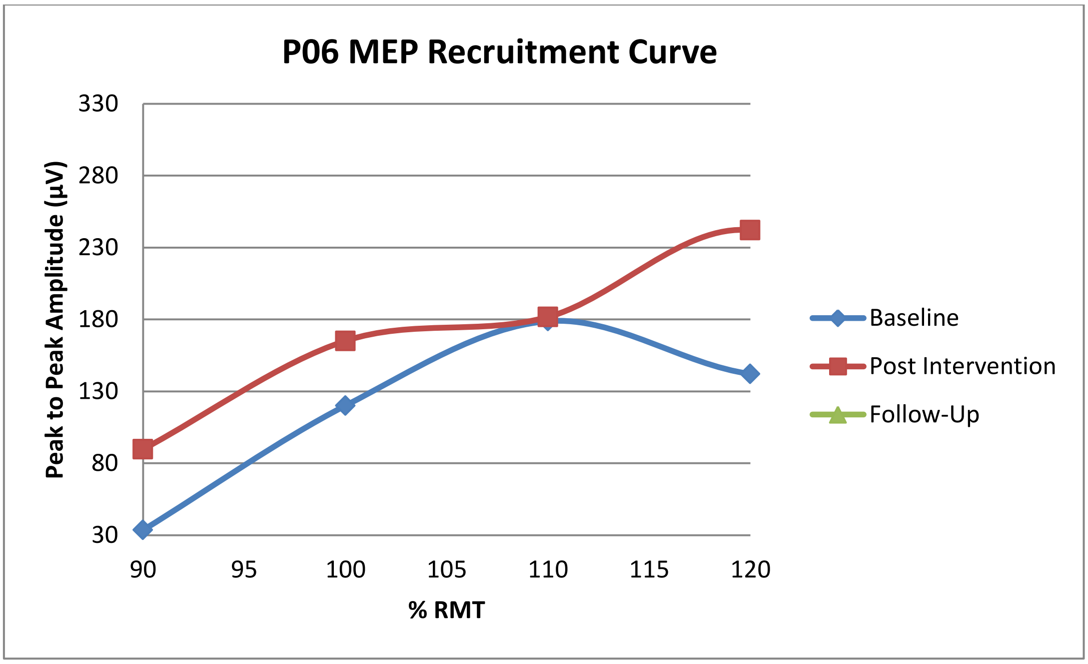


Figure 4.33 MEP recruitment curve of extensor digitorum muscle at baseline, post-intervention and follow-up of P06

4.7.7 Results of the Armeo® data captured during the sessions

Two assessments were carried out during the first five minutes of each intervention session by 16 participants. The first assessment measured the Hand-Path Ratio (HPR) (calculated by dividing the length of the movement trajectory by the most direct path between the start and target locations e.g. a HPR of one would be a straight line between points; a HPR of two means that the performed trajectory was twice as long as the straight line from start to target and therefore had poor coordination). The mean and SD HPR score for the whole sample was 1.56 (SD 0.29) for the first session and at the final session it was 1.30 (0.12) (Figure 3.4). For the whole sample, when paired-samples t-test was applied to the HPR data between the first and final Armeo® session a significant difference (p=0.002) was found. For the real group, the mean HPR scores for the first and last session were 1.49 (SD 0.29) and 1.28 (SD 0.15) respectively. For the sham group the mean HPR scores for the first and last session were 1.61(SD 0.30) and 1.45 (SD 0.45) respectively.

The second assessment, called 'A-Goal' was also carried out after the vertical catching. Two tasks were analysed for this assessment at the three difficulty levels: level two, level three and level four (the latter being the hardest). The tasks analysed involved measurement of shoulder flexion and elbow extension of 16 participants.

The shoulder flexion angles for the first and final robot session for both real and sham groups are presented in Table 4.19. The data was not split up in sub-acute and chronic groups due to the small number of participants in the sub-cute stage carrying out the assessment. A more positive value indicates an increase in shoulder flexion. Non-significant differences were shown between the real and sham group and also non-significant differences in shoulder flexion from the first to the final assessment session.

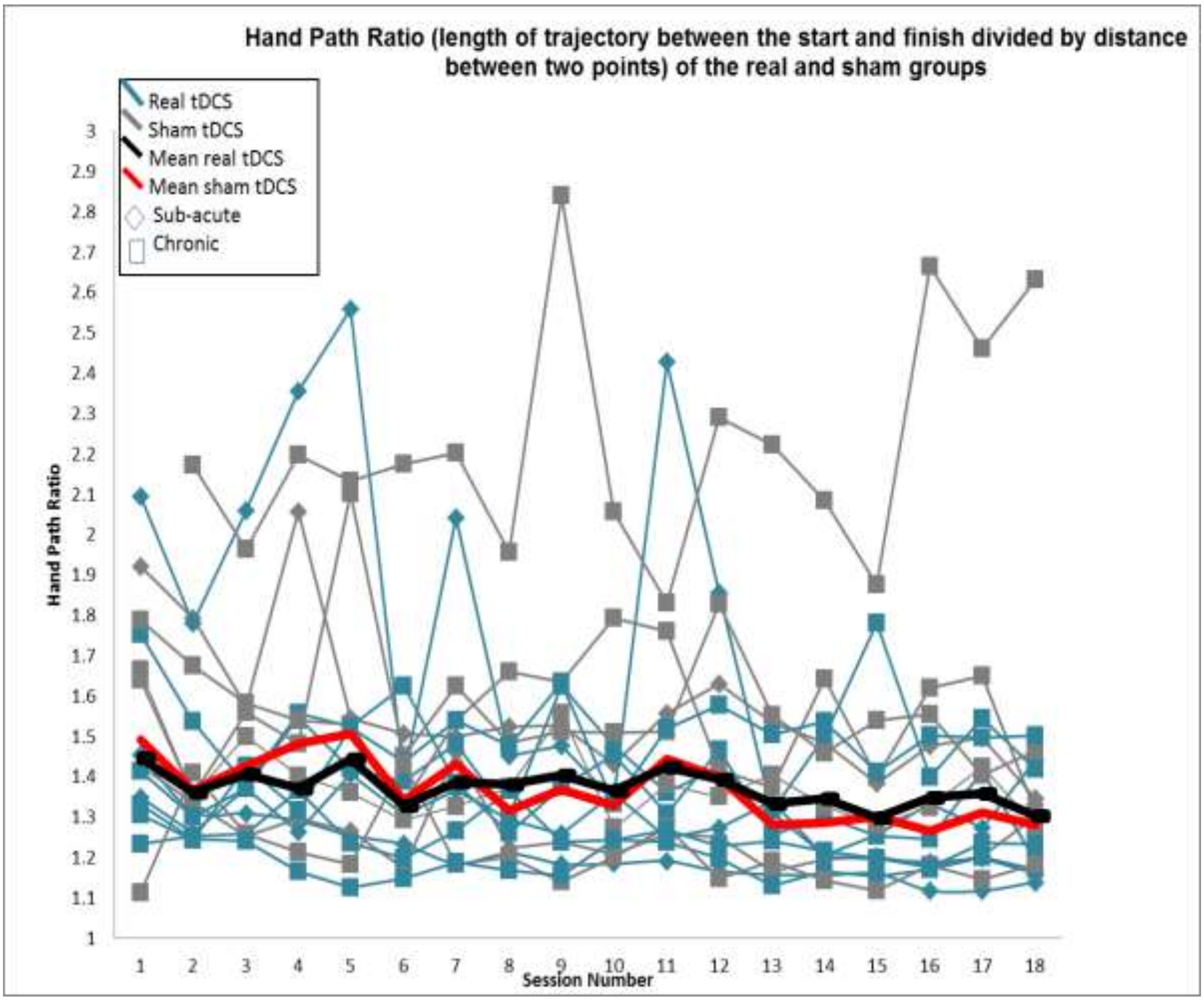


Figure 4.34 Hand path ratio (length of trajectory between start and finish divided by distance between two points) measured at the beginning of each robot session for 18 times for 16 participants

Table 4.19 Mean shoulder flexion angles during first and final (18th) robot assessment of the real and sham groups

	First Assessment Session	Final Assessment Session	Change*1	p-value*3
	(B) (º)	(P) (º)	(P-B) (º)	(P-B)
Overall Mean (SD)*2	-9.33 (17.20)	-6.26 (14.64)	+3.07	0.40
Real Group Mean (SD)	-6.77 (15.72)	-6.86 (14.91)	-0.09	0.98
Sham Group Mean (SD)	-11.88 (17.17)	-5.66 (13.37)	+-6.22	0.25

***1 Change=% from the Maximum Score (5 points), *2 SD= Standard Deviation, *3 *Paired Samples t-test= Significant at p=≤0.05**

In fact, from Figure 4.35 it is noticed that some participants had decreased or increased shoulder flexion during the final assessment session.

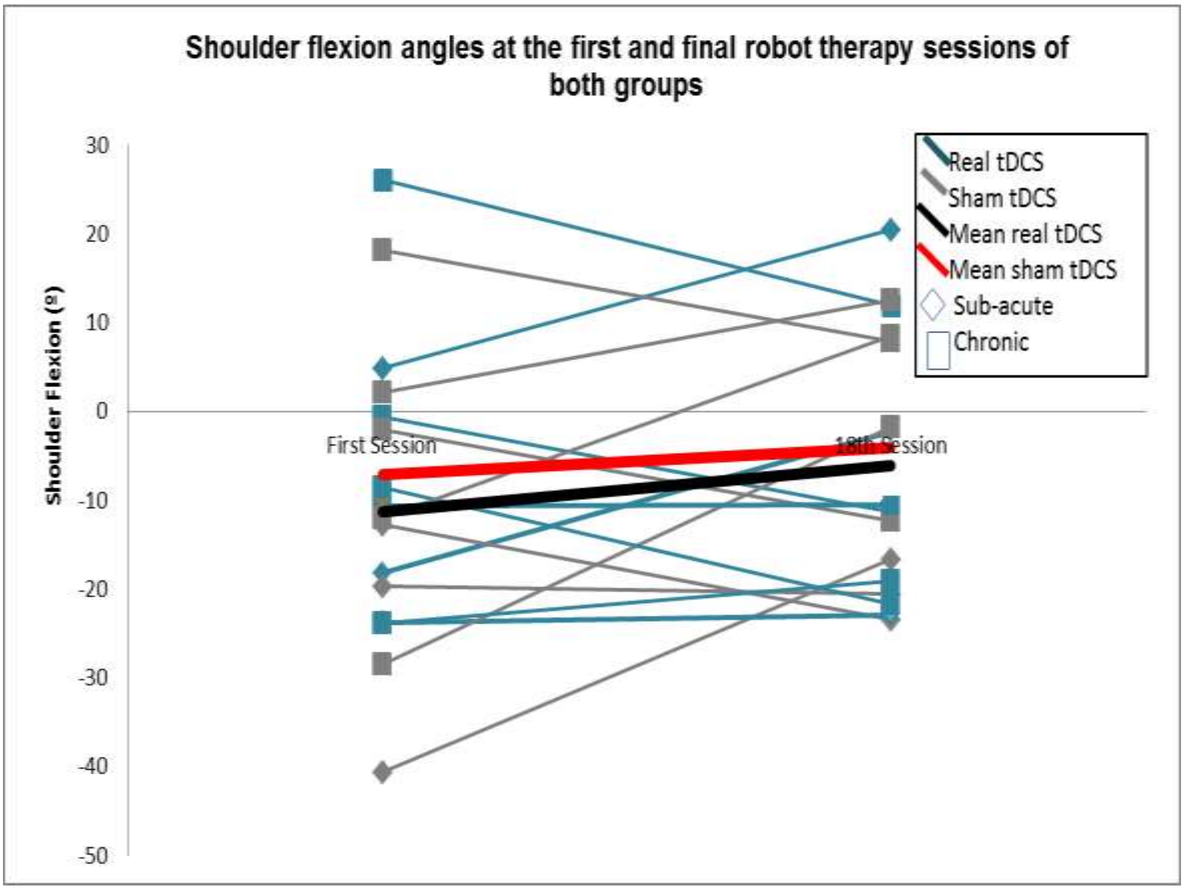


Figure 4.35 Shoulder flexion angles of both real and sham groups at the first and final robot sessions

The elbow angles for the first and final session of the task are presented in Table 4.20. The more positive the value, the greater is the increase in elbow flexion. From the mean values, it was noticed that the participants had increased elbow flexion during the final session compared to the first. A significant difference was found in the sham group in elbow flexion compared to the real group.

Table 4.20 Mean elbow angles elbow flexion angles during first and final (18th) robot assessment of the real and sham groups

	First Assessment Session	Final Assessment Session	Change*1	p-value*3
	(B) (º)	(P) (º)	(P-B) (º)	(P-B)
Overall Mean (SD)*2	-6.32 (75.28)	5.54 (80.38)	+11.86	0.07
Real Group Mean (SD)	-0.68	+6.28	+6.96	0.46
Sham Group Mean (SD)	-11.97 (66.01)	4.80 (77.67)	+16.77	0.03*

***1 Change=% from the Maximum Score (5 points), *2 SD= Standard Deviation, *3 *Paired Samples t-test= Significant at p=≤0.05**

From Figure 4.36, it was noted that elbow flexion angles remained constant from the first to the final robot session.

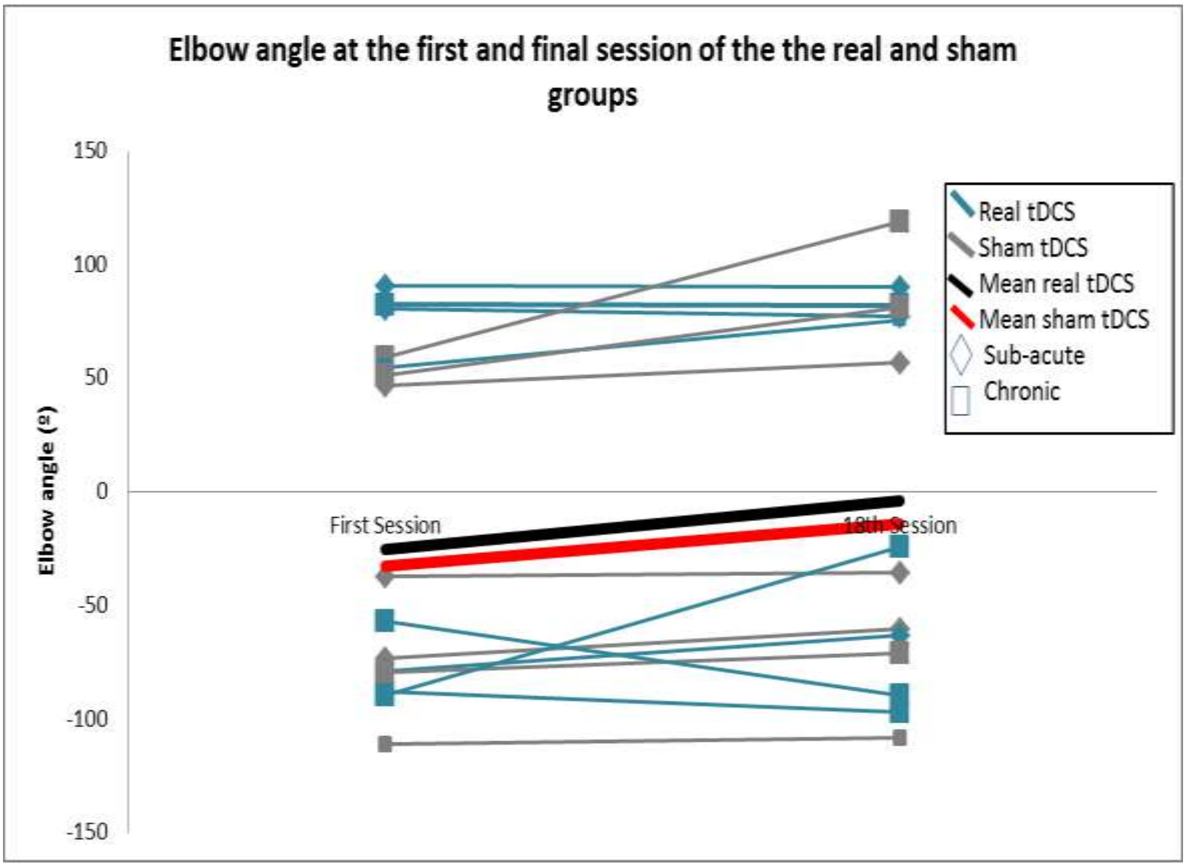


Figure 4.36 Elbow angles of both real and sham groups at the first and final robot sessions

4.7.8 Adverse events and compliance

Case record forms used to record participant details can be found in the Appendix. After each tDCS session, participants completed the tDCS questionnaire and reported any adverse events. One participant (CP6) experienced an adverse event (pain when the tDCS was switched on, and also a first degree skin burn under the area of the positive electrode (1 cm^2) on his fourth intervention session. Following a joint decision between him and the researcher, he withdrew from the trial. This adverse event was reported to the Chair of the Ethics Committee and the Research and Development Department. On follow-up via telephone, the participant stated that the burn had healed after two weeks.

The participants that received real anodal stimulation reported mild to moderate itching during every session. Pain and burning sensations under the electrodes were felt which lasted till the middle or end of the sessions during the first two-five sessions. Three participants agreed that this affected their performance. Details about these sensations are presented in Table 4.21

Table 4.21 Sensations of real anodal stimulation

Sensation	% of the participants receiving real stimulation (n=12)
Mild to Moderate Itching	58
Mild to moderate tingling	58
Mild to moderate warmth	58
Mild to considerable burning	50
Mild to strong pain	42
Light flashes	33
Headaches	8

Participants receiving sham tDCS reported also mild itchiness, tingling and light flashes at the beginning of the session (Table 4.22).

Table 4.22 Sensations of sham stimulation

Sensation at the beginning of the session	% of the participants receiving sham stimulation (n=11)
Mild to Moderate Itching	45
Mild to moderate tingling	73
Mild burning	27
Mild pain	18
Light flashes	27

After the intervention sessions, the participants mainly reported fatigue (55%), but also neck and hemiplegic shoulder pain which lasted on average two days. Two participants with sub-acute stroke complained of pain beyond 90º shoulder flexion at the impaired shoulder which they reported at the start of the trial and during the whole intervention programme. One participant with sub-acute stroke complained of wrist pain which lasted 4 weeks. The pain was treated by their GP with analgesic medication and a cortisone injection. The researcher monitored the pain during these sessions and participants were asked if their pain increased at the end of the individual sessions by rating it on the Visual

Analogue Scale. However, the participants reported decrease in pain after the sessions. Details about these sensations are presented in Table 4.23.

Table 4.23 Sensations and symptoms of the intervention sessions

Sensation	% of the sample (n=22)
Fatigue	55
Shoulder pain of affected side	32
Upper trapezius pain of affected side	14
Shoulder pain of the non-affected side	9
Wrist and hand pain	5
Hand stiffness	5
Bruising on the skin on affected abdomen	5

Participants complained of upper trapezius strain (14%) and when this occurred, the level of support on the RT was increased until their pain subsided. One participant complained of bruising on the affected side of the abdomen. During repetitive shoulder internal rotation and adduction on the robot, part of the equipment caused friction to the abdomen area. This problem was resolved by applying extra padding using adhesive bandaging.

Twenty participants completed the trial in 8 weeks. Two participants in the sub-acute stage deviated from the protocol (P05 and P10) and completed the trial in 10 weeks. These participants found commuting to the University or the Hospital three times a week very tiring and therefore, came to the laboratory twice a week. The baseline assessments were carried out on average three days prior to the intervention programme. The post-intervention assessments were carried out on average two days after the last intervention session. All participants attended the three month follow-up assessment session. The next three sections present the clinical and the neurophysiological findings and the data captured from the Armeo®Spring robot during the intervention sessions.

4.7.9 Summary of quantitative results

This chapter presented the quantitative results of the pilot RCT with a feasibility component.

In summary the following results were demonstrated:

- 22 participants completed the trial and continued their concomitant treatment
- One participant dropped out of the trial due to an adverse reaction to tDCS. Participants in both groups reported sensations of itching, burning, warmth, pain, light flashes were reported. In the sham group these sensations were reported during the first few seconds of the stimulation. One participant receiving real stimulation also reported headaches after the stimulation.
- Overall, the intervention had a significant effect (p=0.000) on the whole sample. However, the null hypothesis was accepted since there was a non-significant effect between the real and sham groups on UL impairments after stroke.
- A statistically significant and clinically meaningful increase in the FMA scores at post-intervention was found in the sub-acute (16%) and chronic (9%) groups (p=0.000 and p=0.01 respectively). Only the participants in the sub-acute group showed a significant improvement at follow-up (p=0.001). It was shown that a sub-cortical stroke was a significant predictor of a higher FMA post-intervention and follow-up score. No significant values were found between the real and sham groups. However a positive trend favouring the real tDCS group on the post-intervention score was reported.
- A statistically significant and clinically meaningful increase of 26% in ARAT scores of the sub-acute group at post-intervention (p=0.03) and follow-up (p=0.05) was shown which means that participants improved in UL function and hand dexterity. The chronic group showed less and non-significant improvement (3.5%) at post-intervention and follow-up. No significant difference was found between the real and sham groups.

- Significant differences (p=0.03) were found in the angle of catch of the wrist flexors of MTS at follow-up compared to baseline scores of the chronic group.
- The sub-acute group had a greater and significant improvement in the MAL scores (20-25%) at post-intervention (p=0.006) and follow-up (p=0.002) respectively) than the chronic group (0.1-3%) at post-intervention and follow-up respectively) which were non-significant. Significant differences (p=0.03) were found for the sham group at post-intervention however non-significant for the real tDCS group for MAL scores for sub-acute group.
- A significant reduction in SIS was found for the real sub-acute group (p=0.001) but non-significant for the sham stimulation at post-intervention for the sub-acute group. Significant differences were found for both the real (p=0.000) and sham groups (p=0.006) at follow-up of the sub-acute group. Non-significant differences were found at post-intervention however, significant differences (p=0.04) were found at follow-up for the chronic (real and sham) groups.
- Non-significant differences were found in HAD in the sub-acute and chronic groups.
- Neurophysiological data of the extensor digitorum muscle from a small sample was analysed. From the data of five sub-acute participants a very high TMS intensity was needed to elicit a MEP Inconsistent results were shown when measuring cortical excitability and therefore it is difficult to draw any conclusions from the results.
- A significant reduction of HPR (p=0.002) was found from the first and final session of RT i.e. better UL coordination. No differences were found in shoulder and elbow flexion angles.

The next section presents the results of the qualitative component of the pilot RCT.

4.7.10 Results - Qualitative component

The same 22 participants took part in the qualitative process. Their demographic details were described in the previous section. A pilot interview was carried out with the first participant. The pilot interview revealed that some participants felt that the questions about non-invasive brain stimulation were all presented in a negative format. The interview schedule was therefore reviewed to provide a more balanced format of both positive and negative questions (Appendix G). The same methodology was then used with the rest of the participants involved in the trial. The following sections will focus on the structured analysis and the themes found from the thematic analysis.

4.7.10.1 Summary of structured questions

All the participants (n=21) replied to the structured questions. The first set of questions focussed on the RT and non-invasive brain stimulation effectiveness (Table 4.24).

Table 4.24 Percentage responses of structured responses about the effectiveness of the treatment programme

Statement about the arm	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I am now more aware of my affected arm	24%	62%	5%	10%	0%
After the research study, my arm feels weaker	0%	5%	10%	57%	29%
My arm feels less tighter	14%	67%	10%	10%	0%
I can reach out with my arm more easily	14%	52%	19%	10%	5%
I can now pick up objects	24%	33%	10%	24%	10%

It is noted that most of the participants were more aware of their arm and felt that their arm was less weak and tighter and they were able to reach better after the trial. However, responses were quite mixed about picking up objects (i.e. hand function) with 57% either strongly agreeing or agreeing and 34% either strongly disagreeing or disagreeing.

Participants were then asked about their experiences of the RT and non-invasive brain stimulation (Table 4.26).

Table 4.25 Percentage responses of structured responses about RT

Statement about robot therapy	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
a) I did not find the treatment enjoyable	0%	0%	10%	52%	38%
b) It was easy to understand what I had to do	38%	57%	5%	0%	0%
c) The target during the robot assessments and games was easy to see	38%	48%	14%	0%	0%
d) The games chosen were beneficial for my weak arm	43%	57%	0	0%	0%
e) I understood the graphs showing my performance	29%	62%	5%	5%	0%

It was found that all participants felt that games chosen were beneficial in helping their weak arm. It was interesting to find that the participants felt that the robot therapy was a positive experience and appeared to agree with the statement implying that they had understood what they had to do. It was also found that the majority (86%) either agreed or strongly agreed that the target during the robot assessment was easy to see. Most of the participants understood the graphs showing their performance.

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Table 4.26 Percentage responses of the structured responses about NIBS

Statement about NIBS	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
a) The stimulation was comfortable	29%	52%	19%	0%	0%
b) The pads placed on my head were comfortable	24%	71%	5%	0%	0%
c) The bandage placed around the electrodes was comfortable	19%	43%	33%	5%	0%
d) The sensation of the magnet coil on top of your head was painful	0%	0%	19%	43%	33%

The majority of the participants felt that the stimulation was comfortable (i.e. 81% either strongly agreed or agree it was comfortable). However, mixed views were expressed regarding the bandage used to hold the electrodes of the tDCS with only 62% strongly agreeing or agreeing it was comfortable. These issues were explored further within the open-ended questions and will form part of the themes and sub-themes found in the qualitative analysis.

4.7.10.2 Themes

Three major themes derived from the open-ended data relating to: A) reflection on participation, B) effects of treatment and C) areas for development.

Figure 4.37 provides an overview of each of the three themes and the related sub-themes. The next section will discuss each theme and the related sub-themes with examples of the participants’ quotes that support each theme.

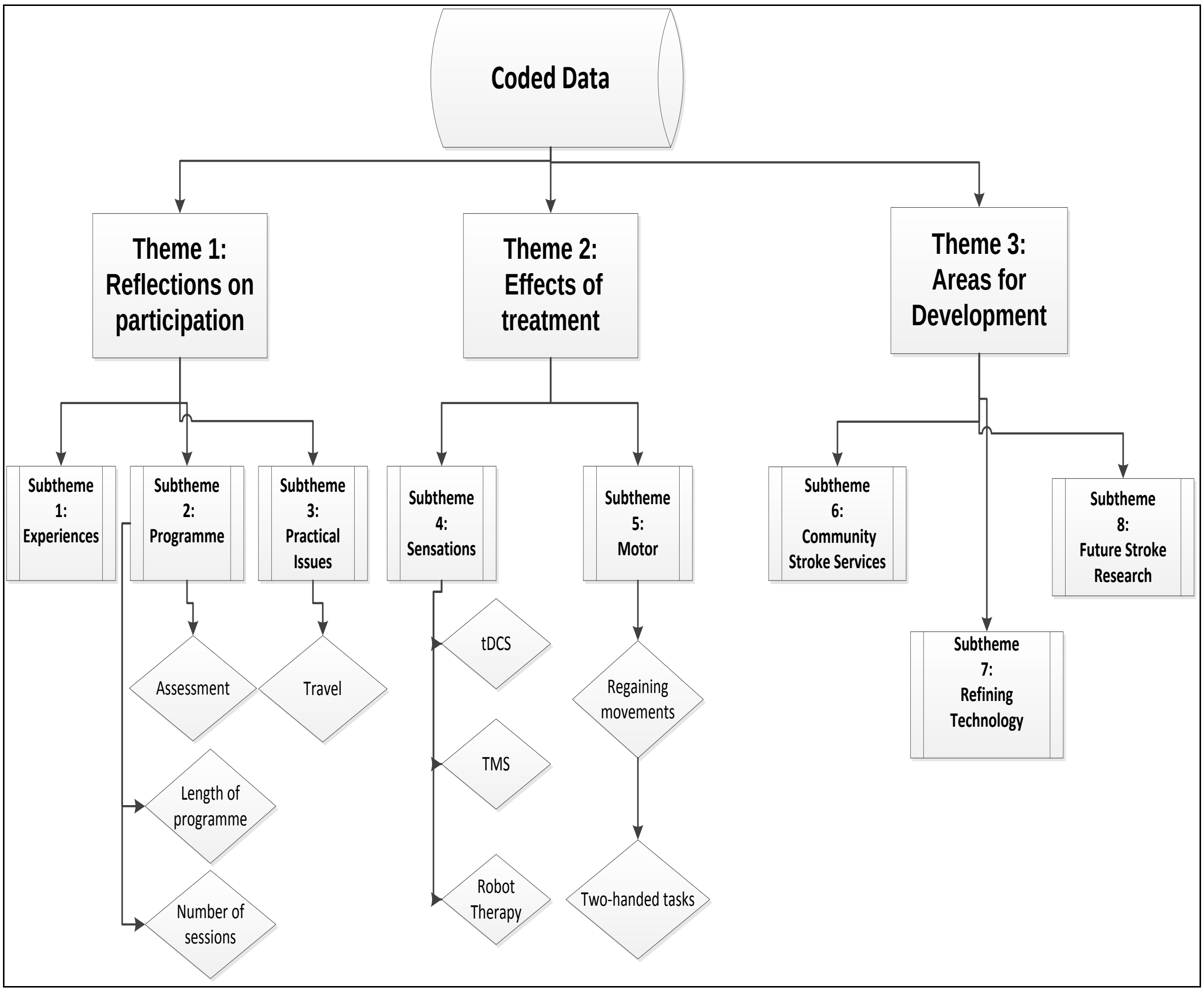

Figure 4.37 A flow diagram showing the major themes with the sub-themes

A) Theme One: Reflection on participation

The participants had time to reflect about their participation in the research trial since the trial lasted for approximately two months. Therefore, one of the main themes was ‘reflection on participation’. This theme focuses on the several important feasibility issues, such as issues related to travelling to the University, and their general experiences related to taking part in the research and being a research participant. Hence, the major sub-themes that were branched out for this theme were i) experiences ii) the programme which focus on the assessment and the intervention programme and iii) practical issues of taking part in the trial such as travel.

<u>i) Sub-theme one: Experiences</u>

When asked about taking part in the research study, the majority of the participants reflected in a positive way and discussed how it was important to them. The participants felt it gave them confidence that ‘someone’ was ‘doing something’ for their stroke.

“It gave me a reason to get up each day… probably it has become like a crutch”

(Lucy, 49 years)

“Only that it gave me the confidence of moving forward from the stroke position that I was in and as I have improved I can either put that down to you know perseverance or the robot you know it is just one of those things a joint thing but I think that that gave me confidence that something was being done you know rather than being left to pull yourself together kind of thing, that sort of thing.”

(Angela, 82 years)

“I think I was lucky, very fortunate to be able to take part”

(Fiona, 72 years)

It was found that although participants discussed how they felt that the treatment programme a “big commitment”, it appeared to give them a focus as they also wanted to improve their UL impairments.

“I realised it wasn’t going to be, what’s the word I am looking for – a cure, but whatever I got out of it was going to be a positive and I have got lots of them out of it. Which makes me a realist doesn’t it, I don’t come here thinking that’s the be all and end all which I am sure some people do”

(Jane, 45 years)

"so in that sense I am extremely grateful for, and again for two reasons, first of all because of the therapeutic the actually therapy from the robot but also it filled my days and kept me off the streets, gave me a focus and that was extremely useful."

(Tony, 68 years)

Participants felt happy about taking part in the research in addition to fulfilling a duty of trying to help people with stroke and improve stroke research.

"yeah I was really happy to do is because I felt it would help me possibly and help people in the future hopefully"

(Tessa, 59 years)

However, before the trial the participants expressed that they were sceptical and had some feelings of 'fear' about the tDCS before the start of the trial.

"The worst feature of it was this vague fear about the technology because years ago I took courses in some psychology and I remember reading about electric convulsive therapy"

(Tom, 69 years)

After the trial, all the participants stated that if they had the opportunity they would use the robot again after the trial. The participants felt that the RT was fun, amusing, interesting, achieving something but sometimes they found it frustrating and difficult. Some also discussed how they thought that it brought out the competitive aspect of their character.

. "I suppose the satisfaction that I did improve gradually over the course of the sessions so sort of personal satisfaction, the worst aspects some of the exercises I did find very difficult and I needed assistance with some of them"

(George, 49 years)

"The best playing the game getting 100% and doing it quicker than the previous time like you know, I mean Lisa would say oh you did that in 3 seconds quicker or you got 100% or you got 100 or whatever and last time you only got and then she would put the graph up on there and say oh you did that two seconds quicker or you know on the graph"

(Jack, 62 years)

The older participants did express that they were not familiar with playing video games and therefore found the first sessions a little difficult.

"I had never paid arcade games before and I can see how people and children get addicted to them because it is a bit of fun to make sure that you are going to shoot so many birds and whatever it is"

(Berta, 79 years)

Participants with sub-acute stroke felt that the research programme was available at the right time of their stroke recovery.

"what had been worked out to be the right time after the stroke and the right time to do any improvements we could do in that time span, because after a certain time apparently it is not beneficial"
(Tessa, 59 years)

On the contrary some participants with chronic stroke stated that they wished that they had this treatment earlier in their recovery process and even though in some cases it was a long time after their stroke, there was still a reminder that they have to still deal with problems of the stroke.

"No. it is a pity I wasn't here earlier on in my recovery,"

(Frank, 71 years)

"very slow extremely slow improvement I suppose even in my case you pray for a miracle and there is a little bit of sadness involved in being reminded that you can't quite wriggle off the hook of the stroke itself"

(Tom, 69 years)

ii) Subtheme two: Programme

Questions were also asked specifically about the feasibility of the assessment and intervention programme and responses relating to these questions will be discussed in further detail in this subtheme.

Assessment process

Most of the participants felt that the assessment session was the right length and without any problems. However, some participants found the process tiring and discussed their frustration about some aspects of the assessment, such as the questions of the SIS outcome measure. For example, they felt that there should have been a better explanation why certain questions were being asked.

"I don't understand the reason for all the questions and tasks so I am just not capable of doing some of the tasks and that's frustrating for me… But I doubt that many stroke patients would be capable of doing many of the tasks, you are talking about using motor control to pick up things"

(George, 49 years)

However, some participants did appreciate the detail of the assessment and could compare the results of the clinical measures involving their UL from the baseline assessment scores.

"No I think they were very good actually, very good, very thorough, you know I can see how much I have improved, or the girls have proved it to me now though you know, I mean people look at me now and they say oh there is nothing wrong with you and what three months ago my arm, well this arm was…it was just wobbling around at the side"

(Jack, 62 years)

Some participants also felt that despite the assessment session being long it was important to be carried out.

"Well it was a bit long but I was quite happy to do it."

(Joan, 71 years)

Treatment programme- Length of the programme and number of sessions

There appeared to be mixed views regarding the length of the treatment programme. Some participants felt it was the right length.

"I think it is probably about right, it is quite intensive in terms of time demand if you, you know including the commuting it was about 6 hours a week"

(George, 49 years)

'By 18 I was beginning to get a little bored with the robot'

(Tony, 68 years)

Some of the participants did not want the programme to end and wanted more sessions, however were concerned that it may potentially lead to some risk.

"I didn't want to stop I just wanted to carry on because there was a certain amount of enjoyment in it as well and I used to look forward to coming here, goodness knows what I am going to do now"

(Jane, 45 years)

Some participants would have liked a longer programme with more sessions.

"yes the twice a week wasn't too bad but three times did become a bit tiring really, that didn't happen very often"

(Fiona, 73 years)

"I think that some people might have more trouble with fatigue, I did encounter with fatigue to some extent but the session, the length of the sessions were ok. I should point out if there were more sessions they would still have to be spaced roughly as they have been for me to cope with the fatigue"

(Tom, 69 years)

All participants stated that the length of each session was just right and that they had enough breaks.

"just about right I think, we used to do 20 minutes and then have a break, the second half was more tiring"

(Fiona, 73 years)

"I didn't feel they needed to be any longer, yeah I would say they were on the right length and from the complexity"

(George, 72 years)

iii) Subtheme three: Practical issues

This basically focussed on the practical issues that were encountered when taking part in the research programme that was not carried out within their own home. Some participants had to travel for a long time to come to the laboratory at the University.

"it is probably three hour travelling time by the time I have waited for trains and got buses"

(Matthew, 51 years)

Some of the participants did not have any means of transport to commute from their home to University. Therefore, they experienced some difficulties planning and paying for their commute.

"Well it is a difficulty my husband can't drive because he is 87 and so I have had to come by taxi and otherwise Lisa sometimes during the holidays brought me by but of course it was two hours because it takes about an hour to go there so it is two hours for her to come and fetch me…"

(Berta, 79 years)

"Travel was the most difficult for us that for my wife it was very difficult really because we had to rely on a whole series of different people you know who have got their own lives to lead and the cost of the taxi to us from where we live was going to be nearly £200 a time, because they charge you waiting time"

(George, 72 years)

On the other hand, participants living close to Christchurch Hospital did not find difficulty travelling to the research site.

“No quite the reverse, transport was provided which has been fantastic.”

(Fiona, 73 years)

No, no we are only ten, fifteen minutes, well fifteen minutes away not from the university from the hospital, from Christchurch hospital

(Jack, 61 years)

Summary of theme one

Theme one has discussed participants’ experiences of being involved in the research study. It has explored reflections on their personal experiences, feelings about the programme and any practical issues encountered. The next theme will focus on the effects of the treatment.

B) Theme Two: Effects of treatment

The effects of treatment were discussed in a lot of detail during the interviews. The effects were seen as being both positive and negative and were experienced both during and after the intervention. This theme was divided into two sub-themes: i) Sensory effects and ii) Motor Effects.

i) Subtheme four: Sensations

The sensations of both tDCS and RT were discussed during the interview. It appeared that the majority of participants receiving sham stimulation did not experience any problems. However, one participant expressed that she wanted to feel more in order to feel the effectiveness.

“like to think that something stronger was being used you know what I mean it was actually, I expected to feel more than I did if you know what I mean so”

(Angela, 82 years)

It was found that some of the people receiving real stimulation did not experience any different sensations.

"Well I didn't notice anything about the brain stimulation, I thought it would be like electric fence with the cattle and things, I thought you would feel something tickling, I was expecting some pain or discomfort not pain, discomfort is the wrong word and I didn't"

(Berta, 79 years)

However, other people receiving real stimulation did report light flashes sensations, but did not feel this was painful. They also added that since they were carrying out the RT during the stimulation these sensations were minimised.

"you know ping and it sometimes a little light in front of my eyes but it wasn't painful or uncomfortable just I just acknowledged it was doing that and that was it because I was too busy looking what was going on, on the screen"

(Jane, 45 years)

"I mean it did sting sometimes, I did flashes in front of my eyes a couple of times and that's a little bit off putting but it is only momentarily, I don't know if there is a better way to do that"

(George, 49 years)

Although the majority of participants did not find the TMS procedure painful, one participant did describe it like a hammer hitting on his head.

"*it was a bit like a hammer when she turned it right the way up"*

(George, 72 years)

Another participant found tDCS so painful that he requested that it should be stopped.

"and painful, very, very painful and my eyes were like on storks"

(Frank, 71 years)

In addition, several participants were concerned that the electricity was put into their brain and they were unsure whether there were any consequences to the treatment.

"The worst bit, I think not knowing what that thing is doing to you brain, when they are shooting them into your head you don't know what it is doing or whether it is doing anything, (affects the nerves and senses but whether it was doing negatives you are looking for positives"

(Richard, 72 years)

With regards to appearance, participants felt it that the montage of the electrodes with the bandages made them feel "odd-looking".

"worst probably I felt a bit of an idiot with it on"

(Lucy, 49 years)

The females in the group did express that it affected their cosmetic appearance and needed to plan their hairdresser appointments accordingly.

"… it messed my hair up"

(Angela, 82 years)

Participants felt RT caused fatigue and sometimes they found it heavy to lift for an hour.

"sometimes if I was tired in the afternoon sessions I would find the robot on the heavy side and difficult"
(Tessa, 59 years)

"I found it really exhausting, I was always exhausted afterwards with the mental effort"

(Joan, 71 years)

One participant stated that he felt the chair uncomfortable and it could be improved if sitting for an hour *“robot arm could be improved, the chair could be more comfortable”*

(Tony, 68 years)

On a positive note, participants felt it provided them the feelings of ‘freedom’ and relieved the heavy weight of her affected UL.

“”And takes the weight of the arm yes, until she start adjusting all the bits and pieces when you do too well”

(Fiona, 73 years)

In addition, one participant felt that the RT decreased her shoulder subluxation and reduced her shoulder pain.

“what it has done is you know you have a ball and socket with stroke people the ball comes out a bit doesn’t it… I don’t know not since I started this all of a sudden I mean I couldn’t lift my arm higher than that without hurting, hello, I have been able to do that for weeks and it doesn’t hurt”

(Jane, 45 years)

ii) Sub-theme five: Motor effects

With regard to motor effects, several participants reported that after each session, they felt an improvement in their daily tasks and thus affecting their quality of life.

“yes I think every session there was improvement in the co-ordination and problems that I was having. I can do lots of things now because of the sessions that I couldn’t do before which is really great it has improved my standard of life no end”

(Tessa, 59 years)

Regaining Movement

Participants mentioned a lot of positive effects of the intervention on their UL. They felt that they were using their impaired UL more often during daily tasks and this appeared to give some participants confidence.

"I feel more confident picking things up and dropping things with my left hand so perhaps it was more I didn't have any control"

(Richard, 74 years)

"'I can open doors and drawers and things better than I could before, pick things up a lot easier, and dressing and undressing has improved because I used to have somebody else help me put my bra on and things like that, I can now sometimes I can, sometimes I can't it depends but more often I can"

(Tessa, 59 years)

Some participants felt that they could do activities they could not do before such as gardening, using a knife, chopping vegetables and picking up objects.

"Peg washing on the line with difficulty but I can do it"
(Fiona, 73 years)

Most of the participants did not feel a difference in their activities immediately after the brain stimulation. In fact, one of the participants stated that probably the RT was contributing to the improvements, rather than the brain stimulation specifically.

"I rather suspect that the very fact of the physiotherapy was at least significantly contributing to the overall affect"
(Tom, 69 years)

However, some participants felt that they performed better during the games when the tDCS was switched on.

"I thought to myself I did better with it switched on because I could feel when it was on I could feel the switch go on and off and I could also feel just a wee bit of warmth from the pads so I sort of knew when it was on and a couple of times I thought to myself I did better with it on than I did with it off"
(Jack, 62 years)

Additionally, some participants felt that the intervention also improved their affected lower limb movement.

"probably for a good 24 hours afterwards not only did my arm you know do what I told it too more you know in as much as it can but my leg was doing it as well and it was nothing to do with my leg, but I could move my leg freer and I found that strange seeing as it was only supposed to be for this… it is like from here to the end of the room for me to get to my toilet, which is the inside porch and I was doing it in half the time because my leg was moving easier"
(Jane, 45 years-received real stimulation)

However, a gentleman with a sub-acute stroke expressed that he did not know whether it was the RT that was the effect of the improvement or whether it was natural recovery.

"So in other words whether any of this or all of this is to do with the robot or just natural recovery I wouldn't know, I am inclined to give the robot quite a lot of benefit since that at least gave a focus to some of the things I was doing"

(Tony, 68 years)

On the other hand, one participant with severe UL impairments expressed that they would have liked to regain more movement than they did.

"I never thought it would be that quick you know, but I hoped to regain a bit more than I have"

(George, 72 years)

Two-handed tasks

The two different groups (sub-acute and chronic) had different views about carrying out two-handed tasks. Participants with severe UL problems did not feel that they carried out two-handed tasks easier after the trial.

“No, not really, I mean basically I don’t do two handed tasks, I have no need for it”

(Frank, 71 years- participant with severe impairments)

“when I stand up after I have been to the loo my posture is better and I am able to pull my pants on and so on using both hands with a far better posture than was ever possible before”

(Tom, 69 years with moderate impairments)

“Tie my shoe laces, hold a piece of wood in my left hand whilst cutting it with a jigsaw with my right, lift a glass to my lips and affectively consume the contents”

(Tony, 68 years- participant with mild impairments)

Participants also expressed that despite being able to grip an object using two hands, they had difficulties with the release of the hand grip.

“but I can hold things in my hands and grip, what I can’t do in un-grip them, we have just proved that because once it is clawed it wants to stay clawed”

(Jane, 45 years)

Summary of theme two

Theme two has described the sensations they felt during NIBS and RT. In addition, improvements and experiences in movement and use of their UL during activities of daily living were also stated by the participants. Participants also discussed how their affected UL is used more often during two-handed tasks. In the following section, the final theme is discussed which focuses on areas of development.

C) Theme three: Areas for development

The previous two themes have described the main experiences, feasibility issues and effects of the treatment. Participants also expressed how they felt current stroke services, the technology and future stroke research could be improved. These will be described in theme three: areas for development. The three main sub-themes within this theme were i) Community stroke services ii) Refining Technology iii) Future stroke research

i) Sub-theme six: Community stroke services

Generally, participants with a sub-acute stroke saw this as the only available rehabilitation service since being discharged from hospital following their stroke.

'that from the time I got out of hospital until just about the end of our sessions with the robot therapy that was the only form of stimulation, rehabilitation treatment, rehabilitation attention I was getting from the system, in other words for the period for the eight weeks, more or less most of the eight weeks since being discharged from hospital I was just absolutely ignored from all elements of the national health service, I didn't get any community service support, I didn't get any support from my GP, I didn't get any support from the hospital and so had I not been doing this I would have been sitting at home well twiddling my thumbs'

(Tony, 68 years)

This shows that there is a lack of community services from the National Health Service in some areas for people with stroke. It was found that many of the participants with sub-acute stroke expressed a feeling of being abandoned.

"someone like me who was full time working, one of the hardest things is suddenly finding yourself at home, unable to do any of the things you used to do, with no focus and as great as it was in hospital with them looking after me you are kind of cast adrift and as a professional woman that just didn't feel right, there had to be some plan and there wasn't one… I got on this, but the first thing I would have got otherwise would have been about four weeks ago my first Physio appointment"

(Lucy, 49 years)

"I am glad somebody is trying to do something you know for stroke patients because I feel you are left to your own devices a lot"

(Carol, 71 years)

Participants suggested that the robot should be integrated with the National Health Service in community or even in the Hospital when it can be used one week after a stroke.

"I think it would be really good to have a system in place like that on the National Health Service for people like me"

(Tessa, 59 years)

"yeah maybe it would be helpful as in the early intervention like in acute management of stroke patients in the first week"

(Tim, 38 years)

ii) Sub-theme seven: Refining technology

The, participants expressed that the technology needs to be improved in order to be integrated in the clinical practice. With regard to tDCS, it was found that some participants did not like the sensation of the bandages that positioned the electrodes around their head. Some participants also reported that the adhesive bandages kept sliding off and therefore suggested it should be replaced by a Velcro strap.

"one thing I would add for the future we need to find a clever less Heath Robinson way on securing the electrodes to the skull, you need to think of some, a little Velcro strap would be the obvious"

(Tony, 68 years)

It was also suggested that a cap or a "head band system" could be developed to help hold the electrodes rather than using adhesive bandages.

'I think it could be improved in the way that the electrodes are held because we did have a lot of problems with the bandages slipping because of my hair mainly and we did work out to put a swimming cap on top of it but perhaps some different way of capping of covering the electrodes would be better"

(Tessa, 59 years)

With regard to the TMS, one participant noted the following:

"sitting a frying pan on top of your head…that's the big one"

(Richard, 72 years)

With regard to RT, most of the participants stated if they had another opportunity they would use the RT again but had certain reservations about the tDCS.

"yes, if it was for sale I would buy it"

(Frank, 71 years)

Well my general reservations about it are still there depending on the case yes I would, depending on the context on which I was contemplating it I think I would probably go ahead yes.

(Tom, 69 years)

Some participants felt that the computer graphics in the games were not accurate and not well designed and appeared to relate to feelings of confusion whilst playing the games.

"I found some of the computer graphic difficult to comprehend and so I didn't perform very well on those particular games as we call them for want of a better word, I didn't think they were particular well designed in terms of graphics"

(Tony, 68 years)

In addition, it was suggested that the graphs displaying the scores after each game should be explained in more detail.

"I am just thinking about the graphs, the graphs could have been possibly explained in more detail, in my particular case as I understood what we were talking about as an engineer possibly for over people it would be more difficult to understand"

(Frank, 71 years)

It was also indicated that some of the games involved an inaccurate workspace and therefore, participants felt the metal part of the robot brushing against their kneein addition to arm straps coming loose.

"I think the hardest thing sometimes was if, if one of the straps sometimes came loose or I mean that's all really little silly things like that, well we had to just tighten it up, or try and do something which involved being low down and I don't know we had maybe thought I had more – for example if you bring it down to do things and they set the work space sometimes you could set the work space and you would think you had only gone as far as your knee so it was fine, but actually then when you tried to do it on the robot to get certain things the work space wasn't as accurate as it looked"

(Lucy, 49 years)

Participants with visual problems were not excluded from the trial, however one participant that did have visual problems did have some problems viewing the target on the computer screen. He suggested that future research should consider this for RT since his vision is now blurred after the stroke.

"I have got a bit of an eye problem in my left eye so I was affected by my condition rather than the fact, I had to put the screen over to the right which Lisa did for me"

(George, 72 years)

The same gentleman also added that for very severely impaired participants there should be the option for the therapist to select which joints to use on the robot during the therapy.

"And the actual arm itself I think the testing could have been separated for those who had a weak shoulder compared to those that have a weak elbow, there are pins in the system so you could just use either or, so in my particular case which is the elbow that's the problem to go most of the side or forward I just use the shoulder where as I need to do this sort of movement but that could have possibly been beneficial"

(John, 63 years)

Participants with severe hand impairments felt that the robot should also focus on moving the hand and releasing the fingers, because this is the main hindrance whilst carrying out activities with their arm.

"but fingers, that's where my problem is at the moment, opening my fingers outwards…I think because my fingers weren't really used, very difficult to let pressure off with my fingers… on the joy stick"

(Tom, 62 years)

There were also suggestions that the grip handle should be less 'sticky' and wider.

"I could have done with the little joy stick being a bit wider or being a bit, it is a bit sort of sticky I could have been a bit more chunky"

(Frederick, 55 years)

Additionally, the word 'robot' was stated to be the incorrect term for lay persons. Since the equipment used for the trial was the Armeo®Spring, it was suggested that it should be referred to as an "articulated splint"

"Choosing the games and perhaps talking about what we might try and get the robot to do, there is a little side aspect to that I think robot is the wrong word for it in particular and I mention this because to my friends who I have been discussing with, I stopped calling it a robot because they and I when I started assumed that the robot would do something, the robot would be motorised and it would move my arm and what I said to them eventually was it was an articulated splint"

(Tony, 68 years)

iii) Sub-theme eight: Future stroke research

Most of the participants valued taking part in research since it will provide a better understanding about stroke showing their altruistic tendency.

"Well I would be willing to take part in any research because if it can progress the understanding of strokes it is worthwhile."

(Joan, 71 years)

"Very happy that there is research going on and I can be part of it, hopefully helping the research"

(Frank, 71 years)

All the participants felt that they would recommend the intervention programme to other people with stroke.

"I think it is a marvellous invention…I think it is a very viable thing and I hope it becomes you know, takes off and becomes introduced"

(Fiona, 73 years)

Therefore, it was suggested that this research should be funded and offered 'nationwide' in order to help a lot of people with stroke all over the country.

"If this could ever get off the ground sort of nationwide think of all those people it could help even if it is… they should give you more money to do more research… if they had more money you would have more robotic arms wouldn't you so maybe you could have a couple of researchers here one end and one and you could get through more people and have a better study and do it in different places, lot of different places."

(Jane, 45 years)

However, participants with chronic stroke did express that funding is a problem because stroke can be a long-term condition.

"the problem is I think resources and cost and the fact that you are talking about a chronic condition you know how on earth if the society as a whole has to pay for it how on earth do you do that in the context of all the other demands on the health service itself"

(Tom, 69 years)

In order, to have a larger trial, participants suggested there should be more technical support for the researchers carrying out a clinical trial.

"*Perhaps there should be more technical back up for the girls… we had one session when the machine broke down on a Friday and there was nobody to give her assistance to see what was wrong with it"*

(Frank, 71 years)

The company that devised the robot are located in Switzerland which can cause problems when waiting for parts for the robot and thus disrupt the trial.

"*Lisa was waiting for a part which meant the arm was slipping*…*you know the arm wasn't working properly and she had to get parts from Switzerland and that kind of thing, so that's the only thing I could say on that"*

(Frank, 72 years)

"the worst aspects was the fact that Lisa was waiting for a part to come and the joy stick kept moving"

(Tessa, 59 years)

They also suggested that future research should have a more-detailed participant information sheet for when participants are approached to take part in a trial. This will help stroke participants have realistic expectations before the research programme begins.

"if you turn round and say we definitely see positive results from people having gone through the process then that was then told to people at the beginning they would be much more relaxed,"

(Richard, 72 years)

"after three or four pages maybe you could have a mixture of videos and text that would belay peoples concerned a sort of Q and A. you know what are your worries about invasive therapy you know, do you understand this, do you understand that and they could split it down into modules"

(Tom, 69 years)

When discussing the RT specifically, it was suggested that future research should involve more patient-therapist interaction. For example, it was suggested that patients should be involved in decisions about setting of the parameters and choosing the games for the therapy.

I think it could probably be improved by more interaction between the therapist and the patient as to what we might achieve with it all, if you see what I mean, lets now try this so you will be exploring the boundaries more whereas this was very much a research project

(Tony, 68 years)

Home rehabilitation was an additional topic that also discussed by some of the participants. They stated that this can be cheaper and avoid problems with travelling to take part in research. It was also suggested that the 'wii system' could be adjusted to be used at home for people with stroke instead of the robot.

"Because I found it useful, if it could be adapted to the wii system you know the wii fit, where you have a nunchuck to move your arm that would be ideal, you could adapt it for people who have a wii or are buying a wii to do exactly the same thing at home in your own time and the repetition for the stroke victim is what you need"

(Frank, 71 years)

"if you were having something new at home would be a help for me because the journey is you know quite tiring"

(George, 72 years)

One participant in fact stated that he is going to build his own robot for his home after the trial

"my partner is going to try and build me a robotic arm, not like that because her Dad might have been an engineer but she is going to do me a wooden one with pulleys and hinges so that I can just practice moving it around she is quite good like that, because I don't want to stop everything just because I have stopped here, there is no point otherwise"

(John, 45 years)

<u>Summary of theme three</u>

The final theme has focussed on current stroke services in the community. Within this theme participants also expressed how future stroke research can be improved in addition to refining health technologies.

4.7.11 Summary of qualitative results

Twenty-two participants were interviewed using a structured/semi-structured process. First interview was piloted and after review the questions were changed or re-structured. After analysis for the structured questions it was indicated that:

- Participants felt major improvements in their arm (82%) however only 57% felt they can pick up objects after the trial.
- Participants also felt that the RT was a positive experience (90%) and the non-invasive brain stimulation was comfortable (81%). However, the participants had mixed views about the electrode montage with the adhesive bandages.

From the coded data, three major themes were developed: a) reflections on participation, b) effects of treatment and c) areas for development

For the first theme, participants felt committed to providing to stroke research and try to improve their UL impairments.

- All the participants felt that if they had another opportunity they would use the robot again. Participants with sub-acute stroke felt that the treatment programme was provided at the right time of their recovery process and participants with stroke expressed that they wish they had this treatment during their sub-acute stage.
- Within the first theme, feasibility issues were also discussed. There were mixed views about the assessment process. Some participants felt it was the right length and detail however some felt it long, tiring and did not understand some of the stages of the assessment.
- Regarding the intervention programme, none of the participants requested less sessions and most felt it was just right in terms of length and amount. Some participants would have liked more sessions. For some, travelling to the university was also an issue.

For the second theme, the sensations experienced by the participants were discussed.

- Some felt tingling sensations and light flashes but it did not bother them however, some participants felt painful sensations.
- The regain of movement and increased use of their affected UL in activities was also discussed. Some participants felt they could carry out two-handed tasks better however, this depended of the severity of UL impairments of the participants.

For the third theme, areas for development were reported.

- The current community stroke services were criticised since a lot of the sub-acute participants felt ‘abandoned’ after hospital discharge.
- They also gave several suggestions of how the technology could be refined such as developing more sophisticated head gear to hold the electrodes and also improving the RT software.
- Suggestions for future stroke research were also provided by the participants. They expressed that more funding for this trial to be nationwide and helping more people with stroke is required.
- Better information should be provided before a participant starts the trial.
- They also discussed that such technology and research should be developed to be carried out at home, such as developing a small robot or a kind of ‘wii-system’.

4.8 Discussion

From the pilot RCT carried out, feasibility issues and the clinical findings need to be discussed. The feasibility of the intervention programme was demonstrated; 22 (96%) participants finished the trial. Nineteen participants (90%) also felt that the RT was a positive experience. However, one participant did experience an adverse reaction from tDCS indicating that such intervention might not be feasible for people with hypersensitive skin. Uncomfortable sensations were reported by the participants during the semi-structured interviews. Participants reported that the bandage supporting the electrodes was itchy, ineffective and not cosmetically acceptable and made suggestions for future research (discussed in chapter 7).

From baseline to post-intervention in this study, participants improved by 10 points in the sub-acute group and 6 points in the chronic group (as measured by FMA) (Gladstone et al., 2002, Page et al., 2012). Therefore both groups showed a minimal clinically important difference in UL impairments. The larger improvement shown in the sub-acute group could be due to natural recovery or the concomitant treatment. The four point difference between the chronic and sub-acute group could result from natural recovery. This will be discussed in further detail in the following chapter.

A trend favouring real anodal tDCS was found from the regression analysis however this was non-significant. This pilot study involved a small sample which could be one of the contributors to the non-significance. Both groups showed an approximately equal amount of improvement from both interventions. This study did not include a third group which did not receive RT. It cannot be determined whether the application of RT or tDCS resulted in the improvement in UL impairments. In addition, another possible confounder was that the baseline FMA score of the sub-acute group receiving sham stimulation was much higher than the participants receiving real stimulation.

The participants in the chronic group did not show an improvement in UL function and dexterity. From the structured responses as part of the interview, only 12 participants (57%) felt that the intervention improved their hand use. Participants with chronic stroke did present with significant differences in angle of catch at the wrist flexors at the three month assessment (measured by MTS). This could be due to decreased use of the wrist and hand after the intervention was completed, resulting in neurogenic or non-neurogenic changes (Pandyan et al., 2005). A significant difference was found in the sham group on UL ADLs of the sub-acute group at post-intervention. This could be due to two reasons. The first was that the sham group had a higher baseline FMA score at baseline and therefore, had less severe UL impairments compared to the real group. The second was that a ‘placebo effect’ could have resulted in the significant difference (Miller and Rosenstein, 2006). However, a significant difference was found in stroke impact in the real group compared to sham group at post-intervention (measured by the SIS). From the third theme of the qualitative data, the participants felt that the trial gave them motivation and encouragement to re-integrate in the community and thus decreasing the impact of their stroke. From this finding, further speculation about the effect of anodal tDCS on stroke impact with a larger sample is required in future research.

Interpreting the results of the neurophysiological data of the present study was difficult and time-consuming due to equipment availability (which is discussed in the limitations section 6.7.3 in chapter six), different individual characteristics and the lack of standardised procedures (Dimyan and Cohen, 2010). The RMT was found in five participants with sub-acute stroke and only for the extensor digitorum muscle. This muscle has a larger representation in the motor cortex and therefore, the MEP was easier elicited. However, no conclusions can be drawn from the results obtained from this study.

Finally from the Armeo® assessments, non-significant differences were found in shoulder and elbow flexion angles of the impaired UL at post-intervention. The global hand path ratio significantly decreased over the robotic intervention, indicating an improvement in coordination in the affected UL. This was the first tDCS study to involve a kinematic measure such as HPR in a RCT research design using a sample of people with stroke. This sensitive measure demonstrated that participants improved their UL coordination after the intervention which was difficult to assess when using the clinical measure, FMA.

4.9 Conclusion

This chapter presented the methodology, results and a discussion of the clinical findings of the pilot RCT study with a feasibility component. The feasibility analysis (including the recruitment process, intervention programme, and project resources) showed that the study was feasible however, checking for adverse reactions from tDCS needs to be integrated in to future work.

The main findings were:

(1) A significant and clinically meaningful effect on UL impairments in the sub-acute and chronic groups which lasted for three months post-intervention for the participants with sub-acute stroke.

(2) A significant and clinically meaningful effect was shown in UL function and dexterity in the sub-acute (but not chronic) group at post-intervention assessment.

(3) A significant difference was found in angle of catch at the wrist flexor muscles of the participants with chronic stroke at the three-month follow-up.

(4) The intervention significantly decreased stroke impact of the people in the sub-acute stage at post-intervention and follow-up but only at follow-up for the chronic group.

(5) Changes in stroke impact and upper limb impairments were supported by the views and experiences of the participants presented in the qualitative results. Participants also gave suggestions how future research can be improved.

(6) Cortical excitability - MEPs of the extensor digitorum muscle were elicited in five participants with sub-acute and sub-cortical stroke. Due to the small amount of data one cannot make definite conclusions about the presented neurophysiological results.

The next chapter will present the reliability study of the MEP response and amplitude measurement involving healthy adults. Chapter six will then present a detailed discussion about the findings obtained from the pilot RCT and the reliability study.

Chapter 5

Intra-rater and Test-retest Reliability Study of Motor Evoked Potential Measurement

5.1 Introduction

Transcranial Magnetic Stimulation (TMS) was used to assess cortical excitability in the RCT using robot therapy with and without transcranial direct current stimulation for the impaired Upper Limb (UL) in stroke. This chapter focuses on assessing the intra-rater reliability of this measurement involving healthy adults. This work adds to knowledge about the psychometric properties of this assessment, and also provides additional context to the conclusions drawn from the RCT.

5.2 Background

Transcranial Magnetic Stimulation (TMS), a non-invasive form of brain stimulation, can be used both as an intervention and an assessment tool. It allows the study of neural mechanisms involved in motor control in healthy people and also people with neurological conditions (Rossini and Rossi, 1998, Fleming et al., 2012). TMS application involves placing a circular or a figure of eight magnetic coil over any area of the cortex. As discussed in Chapter two, TMS in combination with electromyography (EMG), motor thresholds and Motor Evoked Potential (MEP) amplitudes are measured as a test of cortical excitability. Temporal stability of TMS assessment is essential for use in clinical trials at multiple time-points (Fleming et al., 2012)

Reliability of a measure refers to the extent the measurement is free from error and also consistent (Cohen and Whitten, 1988). A reliable measure provides confidence that changes observed in the measure are due to physiological changes and not due to poor reliability in the measure itself (Christie et al., 2007). Test-retest reliability is the assessment of the consistency of the variable measurement by one rater on two different occasions and intra-rater reliability refers to the stability of the data measured by one rater across two or more trials on the same day (Portney and Watkins, 1993).

Precise placement of the coil is fundamental as both the orientation and position can affect the MEP response (Mills et al., 1992). However, few studies have explored the reliability of the TMS measurement. The intra-rater and test-retest reliability TMS measurement of cortical excitability showed good to excellent reliability (ICC=0.60-0.92) when measuring MEP thresholds however low intra-rater reliability for MEP amplitude of hand muscles in young adults (ICC = 0.01 to 0.34) (Livingston and Ingersoll, 2008, Kamen, 2004). However, high intraclass correlation coefficients were found in young adults for the biceps brachii MEP amplitude (ICC=0.95-0.99). A potential limitation of the latter study is that a circular coil was used which is less focal than the figure of eight coil (Rösler et al., 1989).

Good to high intra-rater reliability (ICC=0.65-0.83) of MEP amplitude measurement of the abductor digiti minimi muscle was found in older adults (Christie et al., 2007). The only study which explored the test-retest reliability of MEP measurement at the hand extensor muscles in 10 chronic stroke participants reported large fluctuations in MEP amplitude between sessions (Butler et al., 2005). However, repeated measures ANOVA were used rather than ICC which is the most appropriate statistical test to assess reliability since it assesses degree of consistency in addition with agreement between ratings (Bruton et al., 2000).

TMS measurement has been shown to be an intra-rater and test-retest reliable method of measuring MEP amplitude and RMT of the hand muscles in young adults. Neuro-navigation equipment was developed to increase measurement reliability by allowing the tracking of the position of the coil in real time (Herwig et al., 2001). The neuronavigation uses Magnetic Resonance Imagining (MRI) scans to identify areas such as the motor cortex in relation to anatomical landmarks (Julkunen et al., 2009).

Intra-rater and test-retest reliability of RMT and MEP amplitudes of the upper arm (Anterior Deltoid [AD]) and forearm (Extensor Digitorum [ED]) muscles using neuro-navigation equipment has never been explored in healthy adults. Two sets of tests were conducted with healthy adults by a single assessor. Participants were age-matched with participants with stroke that took part in the pilot RCT (38-79 years old) which was described and discussed in chapter four. Set one tests were conducted one hour apart (intra-rater reliability) and set two tests were conducted three days apart (test-retest reliability).

5.3 Research question

What is the intra-rater and test-retest reliability of the TMS assessment of the MEP threshold and amplitude of the AD and ED muscles in healthy adults?

5.3.1 Hypothesis

The MEP threshold and amplitude of the AD and ED muscles on the different occasions in healthy people will show acceptable reliability with ICC values of more than 0.75 on the same day and separate days (Fleiss 2011).

5.3.2 Aim and objectives

The main aims for this study were to:

a) Quantify the experimental error (intra-rater reliability) which can be tested by repeating tests with a short interval (during which the subject's cortical activity is unlikely to have changed)

b) Identify the experimental error plus the variability due to natural day-to-day changes in cortical excitability (test-retest reliability).

The objectives of the research were:

- To quantify the intra-rater reliability of the MEP threshold and amplitude of the AD and ED muscles measurement by repeating tests within an hour
- To test the test-retest reliability of the MEP threshold and amplitude of the AD and ED muscle measurement by repeating tests three days apart
- To compare the reliability of measuring MEP responses on the right and left motor cortex

5.4 Method

A quantitative reliability study was conducted using a convenience sample of healthy adults.

5.4.1 Materials

The same equipment for the cortical excitability measurement of the Randomised Controlled Trial (RCT) was chosen: Magstim® 200^2 TMS in combination with the Brainsight® (CE marked) neuro-navigation equipment. To measure the MEP response, the TMS equipment was interfaced with the Electromyography equipment (Biometrics Ltd). This was described in detail in section 4.2.4.1 starting on page 96.

5.4.2 Participants

With the aim of age-matching the participants with stroke that took part in the RCT, healthy adults with similar ages were recruited. The inclusion and exclusion criteria were the following:

Participants needed to be:

- >18 years
- Able to provide informed consent

Participants were excluded if they:

- Had impaired gross cognitive function; score of less than 24 of the Mini-Mental State Examination (Folstein et al., 1975)
- Had a neurological condition such as stroke
- Had a history of epilepsy
- Had implants within the brain
- Had had previous brain neurosurgery
- Had metal implants in the head including cochlear implants
- Were taking medications that influence cortical excitability
- Have had previous adverse effects with TMS
- Were pregnant

Participants were recruited through the University of Southampton website, participant databases of the Faculty of Health Sciences and Psychology and community groups. Potential participants were given an information pack via mail or email. The pack contained a participant letter, a participant information sheet, a reply slip and a pre-paid envelope (Appendix B.2). Interested participants returned the reply slip to the main researcher (LTT). They were then contacted to arrange an appointment at the Laboratory of the Faculty of Health Sciences at the University of Southampton.

5.4.3 Randomisation

Block randomisation was used. An external researcher carried out a block randomisation process using a computer program called ‘random allocation software’ (Saghaei, 2004). The program created blocks of four of either left or right cortical stimulation. The same researcher placed the printed papers of left/right in sealed envelopes in batches of four.

Each participant was randomised into group A or B.

- Group A: Left cortical stimulation
- Group B: Right cortical stimulation

5.4.4 Procedure

The researcher (LTT) and her assistant (Ms Amy Din), a clinical scientist, greeted the recruited participants at the laboratory. Any questions about the study were answered and if the participant agreed to take part, they were asked to sign a consent form (Appendix D.5). Demographic data including age and handedness were recorded. This ensured that the participant satisfied the selection criteria. A TMS questionnaire was used to ensure that the participant fulfilled the criteria for TMS application (Rossi et al., 2011) (Appendix E.3.3). If the participant answered ‘yes’ to any of the questions, the team neurologist (Dr Malekshmi Desikan) was consulted accordingly. In order for the participant to give informed consent, an assessment of cognition using the Mini-Mental State Examination (Folstein et al., 1975) was carried out. If the participant met all the criteria, the study was then commenced. A sealed envelope from the randomisation process was handed to the participant and he or she opened it to find out which group they had been allocated to.

The measurement was carried out in the same order as explained in the procedure sub-section of the ‘assessment section’, 4.2.4.1. The experimental set-up is detailed in Figure 5.1. The only difference from the procedure carried out for the pilot RCT, is that the cortical stimulation was carried out on either the left or right side of the brain. Therefore, if they were allocated to the left cortical stimulation group, the EMG electrodes were placed on the right AD and ED muscles and vice versa if they were allocated to the right cortical stimulation group.

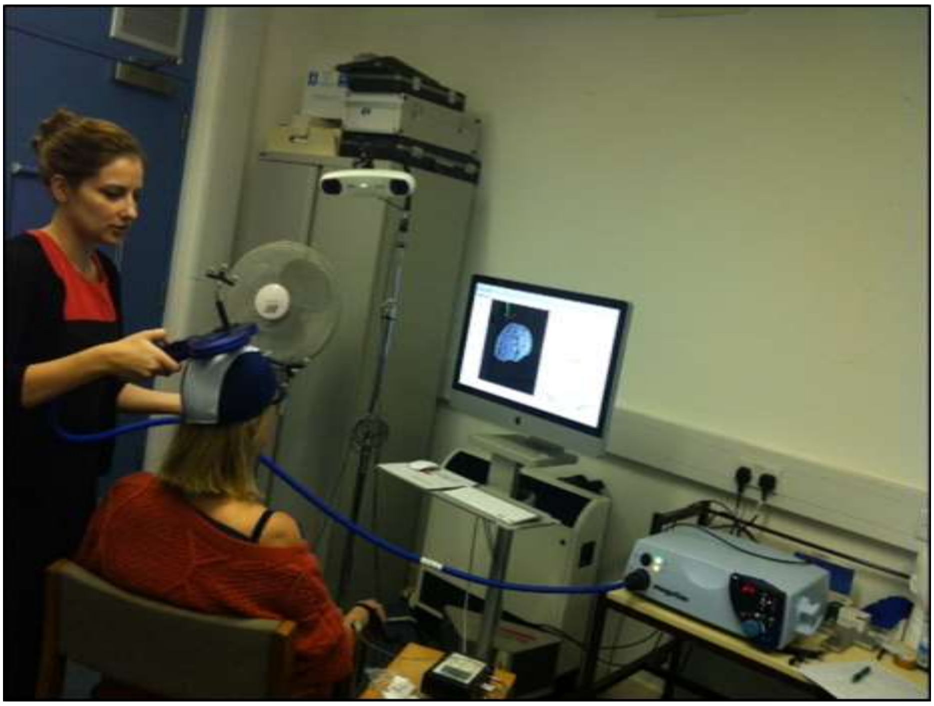

Figure 5.1 Demonstrating the experimental setup:

The TMS equipment, Brainsight® and EMG equipment-The figure of eight magnetic coil was placed on the participant's head to measure MEP responses of the anterior deltoid and extensor digitorum muscles by EMG

The measurement procedure was carried out on three occasions with each participant by the same assessor (LTT). Two measurements were carried out on day one with 30 minutes rest in between (to reduce the possibility of nerve accommodation (Chen and Rothwell, 2012) and the third measurement was carried out three days later.

5.5 Ethics

Ethical approval was obtained from the Faculty of Health Sciences Ethics Committee (Ethics Number: 5382) (Appendix C.9).The protocol followed the TMS safety guidelines, published by the Safety of TMS Consensus Group (Rossi et al., 2009). Each participant gave written informed consent for taking part in the research. It was also ensured that any information related to the participants was kept anonymous and confidential and privacy was also ensured throughout the research. Each participant had the option to withdraw from the study at any time. At the Laboratory of the University of Southampton, (after giving informed consent), participants could have faced some anxiety. The researcher (LTT) is a physiotherapist registered with the UK Health Professions Council and therefore experienced and competent in interacting with people undergoing interventions. If the participant experienced discomfort or anxiety during intervention at any time the researcher stopped data collection, monitored and reassured the participant. If the distress continued, the procedure was stopped.

The researchers were present in the Laboratory at all times during the study. Recruited participants were informed of possible side effects and the researcher asked the participants at the end of every session and before the start of the third session whether any side effects occurred. In case of adverse effects and for any medical advice, liaison with the neurologist on the research team (Dr Malekshmi Desikan) was to be sought and appropriate action taken.

5.6 Overall project funding

This project was partially funded by the Wessex Medical Research and Maltese Government with collaboration from European Union. The funding was used to purchase the TMS and neuro-navigation equipment and for participant travel reimbursement.

5.7 Data protection and anonymity

Electronic data was stored on the password protected University computer network. Personal address details were written in the reply slips filled in by the participants. These documents were kept in a locked filing cabinet in the research unit. All anonymised data will be stored for 10 years according to institutional rules. During the study, every participant received a personal participation identification number that was used during data collection and for data storage on electronic files on University computers. Computer files were saved on the University network and password protected.

Only members of the research team (LTT, Jane Burridge, Ann-Marie Hughes and Ms Amy Din) had access to the personal data.

5.8 Data and statistical analyses

The data was exported from the DATALOG program to a ‘txt’ file. These files were then inputted into the software program MATLAB R2013b (32-bit). A program was written by the Experimental Office of the Faculty of Health Sciences (Dr Martin Warner) and this program was used to measure the peak to peak amplitude of each MEP. The data was inputted into Microsoft Excel 2010 and the mean peak to peak amplitudes of five MEPs of both muscles at 100 to 150% of RMT on the three different occasions were calculated. The data from 110-150% was normalised according to the 100% MEP amplitude (110-150% divided by 100% MEP Amplitude).

Statistical support using IBM SPSS Statistic 21 was provided by Dr Sean Ewings from the Southampton Statistical Sciences Research Institute of the University of Southampton. Repeated measures ANOVA was carried out between tests and these were all found to be non-significant. The data was normally distributed, so the reliability of the RMT and MEP amplitudes of both muscles was analysed using two-way mixed model (Model 3,1) Intraclass Correlation Coefficients (ICCs) at a 95% Confidence Interval. The ICC for single measures was reported. Bland-Altman plots for RMT and MEP amplitudes were then plotted using Excel in order to analyse the agreement between tests 1 and 2 and tests 1 and 3 (Rankin and Stokes, 1998). The interpretation for the ICC as described by Fleiss (1986) was used; 0.4 indicating poor, 0.4 to 0.75 indicating fair to good and 0.75 indicating excellent agreement (Fleiss, 2011).

After obtaining the ICCs, the Standard Error of Measurement (SEM) was calculated between tests 1 and 2 and tests 1 and 3. The SEM is a reliability measure of response stability which is calculated by estimating the standard error in a set of repeated scores (Watkins and Portney, 2009). It is calculated on the basis of sample data using the sample SD and the sample reliability coefficient, in this case the ICC.
Therefore the following formula was used:

$$\textbf{SEM= SD } \sqrt{1 - ICC}$$

The SD value was the average of the SD values obtained for tests 1 and 2 or tests 1 and 3. The Minimal Detectable Change (MDC) represents the smallest difference or change that would be over a given period of time required to be considered statistically significant. After the SEM was calculated, the MDC was calculated for tests 1 and 3 using the following formula (Stratford, 2004):

$$\textbf{MDC= 1.96 x } \sqrt{2XSEM}$$

The SEM and MDC were calculated for the RMT and MEP amplitudes at the 100-150% TMS intensitiesof RMT for both the ED and AD muscles. The data of the ED muscle was split into left and right group cortical stimulation. The level of reliability was compared for RMT and MEP amplitude for both groups. In addition, the same data was also split up into young adult (38-59 years) and older adult (60-79 years) groups (an older adult has defined by the World Health Organisation as 60 years and older). The level of reliability for RMT and MEP amplitude at 100% RMT was also compared between both groups.

5.9 Results

Twenty-two participants took part in the study which has been suggested as an appropriate number for reliability studies (Atkinson and Nevill, 1998). The sample consisted of 11 (50%) males and 11 (50%) females, with a mean age of 59.86 years (SD 11.7). They all achieved a score of >24 on the MMSE.

Two participants did not complete the study; no MEP responses were elicited for R09 and R02 did not attend the third session due to eye twitching sensations. Therefore, 20 participants completed the whole study and the data represents 11 participants received left cortical stimulation and 10 participants received right cortical stimulation. Data for the two sessions of R02 was pooled with the rest of data from the 20 participants that completed the study. Two participants from the whole study reported dizziness and headaches after the first session which subsided after an hour.

Table 5.1 Demographic data of recruited participants

Participant ID Number	Gender (F/M*[1])	Age (years)	Hand Dominance (R/L*[2])	Stimulated Hemisphere (R/L)	MMSE*[3] Score (out of 30)
R01	M	50	L	R	29
R02	M	71	R	R	27
R03	F	55	R	R	29
R04	F	70	L	L	30
R05	M	52	R	L	28
R06	F	45	R	R	30
R07	M	38	R	L	30
R08	F	46	L	R	30
R09	F	75	R	R	29
R10	M	79	R	L	30
R11	M	71	R	L	28
R12	M	68	R	R	28
R13	M	79	R	R	29
R14	F	60	R	L	30
R15	M	48	R	L	28
R16	M	69	R	L	29
R17	F	50	R	R	28
R18	F	57	R	R	30
R19	M	61	R	L	29
R20	F	59	R	L	30
R21	F	63	R	R	30
R22	F	51	R	L	30
% or Mean (SD)	**50% M 50% F**	**59.86 (11.70)**	**13% (L) 87% (R)**	**50% (L) 50% (R)**	**29.14 (0.94)**

*[1]M=Male and F=Female, *[2] R=Right and L=Left , *[3]MMSE=Mini-Mental State Examination

5.9.1 Resting motor threshold and motor evoked potential amplitude

The results of the resting motor threshold measurement of the AD and ED muscles on the three occasions are presented in Table 5.2.

Table 5.2 Resting Motor Threshold of the anterior deltoid and extensor digitorum muscles of the three measurements

	Day One				Day Two	
Participant Id Number	**RMT*[1] Test 1*[3]** (%)		**RMT Test 2*[3]** (%)		**RMT Test 3*[4]** (%)	
	ED	AD	ED	AD	ED	AD
R01	60	NE*[2]	66	NE	58	NE
R02	42	NE	42	NE	DO	DO
R03	59	NE	59	NE	58	NE
R04	41	68	38	62	40	84
R05	59	NE	59	NE	58	NE
R06	60	89	67	89	61	NE
R08	59	NE	60	60	60	60
R10	64	84	63	87	63	86
R11	68	84	68	75	69	84
R12	68	NE	78	NE	72	NE
R13	71	NE	75	NE	77	NE
R14	39	51	40	52	49	63
R17	70	77	70	77	80	88
R18	66	NE	69	NE	70	NE
R21	68	NE	77	NE	61	NE
R22	56	74	53	74	59	74
R23	68	89	58	88	60	NE
R24	48	79	47	75	54	75
R25	59	84	53	80	48	80
R26	52	72	51	69	55	72
R27	49	75	52	66	52	75
Mean (SD)	**58.38 (9.87)**	**77.17 (10.59)**	**59.29 (11.82)**	**73.38 (11.34)**	**60.20 (9.81)**	**76.45 (9.13)**

*[1]RMT= Resting Motor Threshold, *[2] NE= Not Elicited, *[3] test 1 and test 2 were carried out on the same day, *[4] test 3 was carried out three days after test1, *[5] DO= Dropped out from study

The mean ED RMT at test 1 was 58.38% (SD 9.87), at test 2 was 59.29 % (SD 11.82) and test 3 was 60.20% (SD 9.81). The mean AD RMT at test 1 was 7.17% (SD 10.59), at test 2 was 73.38% (SD 11.34) and test 3 was 76.45% (SD 9.13). In all cases, the AD RMT was higher than the ED RMT. Due to maximum intensity TMS output of 100%, the high intensity needed for AD RMT made it impossible to measure recruitment curves at 140-150%.

Figure 5.2 depicts the recruitment curves from 100-150% of the RMT of ED muscle of the participants. The mean MEP amplitudes and shape of the curves were very similar between tests 1, 2 and 3.

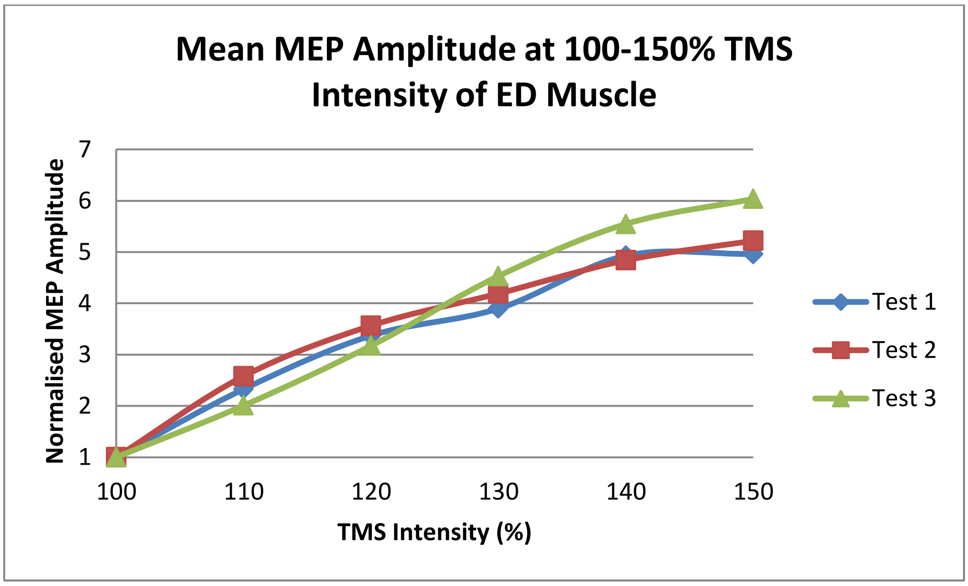

Figure 5.2 Recruitment curves of extensor digitorum Muscle at tests 1, 2 and 3

Figure 5.3 depicts the recruitment curves from 100-130% TMS intensity of the AD muscle of all the participants. The mean MEP amplitudes and shape of the curves between tests 2 and 3 were very similar up to 110% of the RMT however, they diverge after 120% of the RMT. However, a different curve shape (smaller MEP amplitudes are noted at 110% of the RMT was noted for test 1.

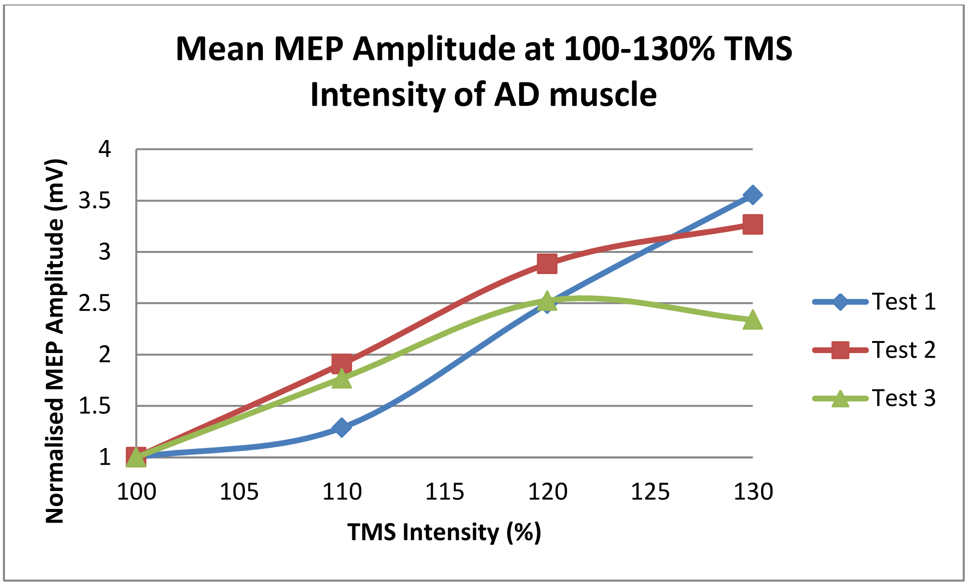

Figure 5.3 Recruitment curves of anterior deltoid Muscle at tests 1,2 and 3

5.9.2 Reliability analysis

Analysis was carried out between tests 1and 2 and tests 1and 3. The latter ensured that no carry over effects influenced the results over separate days. Interclass coefficients and Bland and Altman were analysed for the RMT and MEP amplitudes.

5.9.2.1 Reliability of resting motor threshold

Reliability analysis showed that the RMT for the ED and AD between test 1 and 2 had an excellent level of agreement (ICC=0.891 and 0.943 respectively). Between test 1 and 3, ED and AD also had excellent level of agreement (ICC=0.841 and 0.769 respectively) (Table 5.3). The MDC between test 1 and 3 for RMT was 10.87% for the ED muscle and 13.14% for the AD muscle.

Table 5.3 Intra-class coefficients with confidence intervals of resting motor threshold of both muscles between tests 1-2 and test 1-3

RMT[*1]	Means (SD)	ICC[*2]	CI[*3]	SEM[*4]	MDC[*5]
Test 1 and 2 (ED)	58.38 (9.87) 59.29 (11.82)	**0.891**	**0.752-.954**	3.58	**-**
Test 1 and 3 (ED)	58.38 (9.87) 60.20 (9.81)	**0.841**	**0.642-0.934**	3.92	**10.87**
Test 1 and 2 (AD)	77.17 (10.59) 73.38 (11.34)	**0.943**	**0.823-.982**	2.62	**-**
Test 1 and 3 (AD)	77.17 (10.59) 76.45 (9.13)	**0.769**	**0.346-0.932**	4.74	**13.14**

*[1] RMT=Resting Motor Threshold, [*2]ICC=Intraclass Coefficient, [*3] CI=Confidence Interval, [*4] SEM=Standard Error of Mean, [*5] Minimal Detectable Change (measured between test 1 and 3)

The differences in RMT of ED muscle between tests 1 and 2 are plotted against the mean values for each participant in a Bland and Altman plot. The middle line shows the mean difference. The 95% upper and lower limit of agreement represents 2SD above and below the mean difference. From Bland and Altman analyses it was noted that there was good agreement between RMT values from tests 1 and 2; data points are spread evenly below and above the mean difference (Figure 5.4). The Bland Altman plots showed one outlier (outside the mean difference ± 2SD).

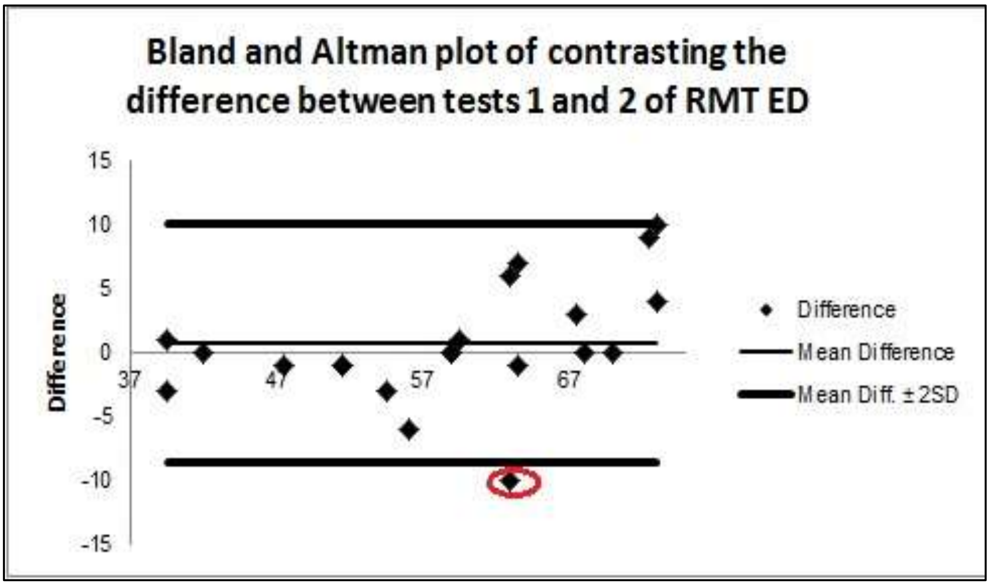

Figure 5.4 Plot of difference in extensor digitorum resting motor threshold between tests 1 and 2
(Red circle represents an outlier)

The bland and Altman plot shows that data points are distributed to the right and that RMT values for test 3 (day 2) were higher than test 1 for the ED muscle (Figure 5.5).

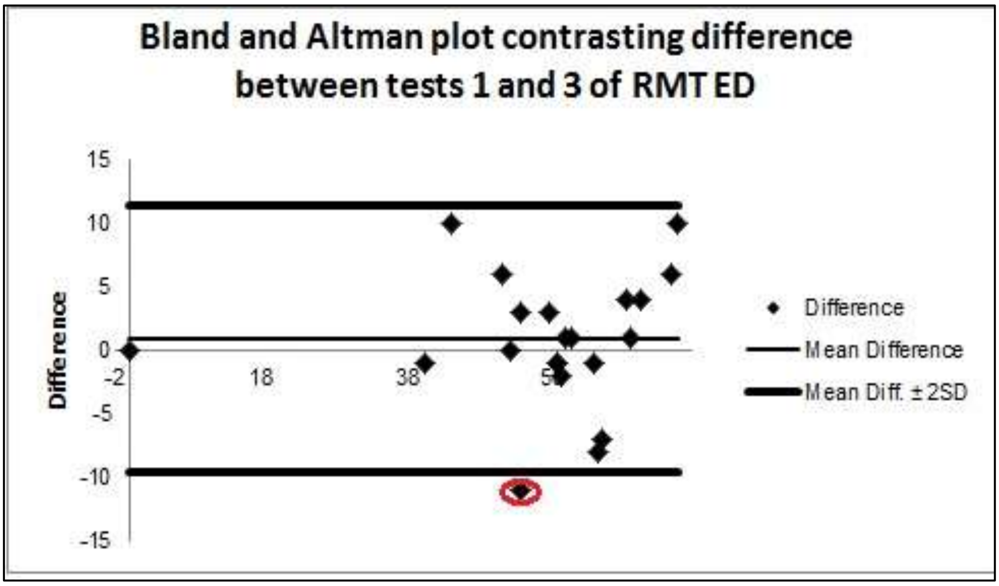

Figure 5.5 Plot of difference in extensor digitorum resting motor threshold between tests 1 and 3
(Red circle represents an outlier)

Less data exist for the AD muscle and the Bland and Altman plots were different than the plots for the ED muscle (Figure 5.6). The data points were clustered to right (less spread of data) and there were two outliers.

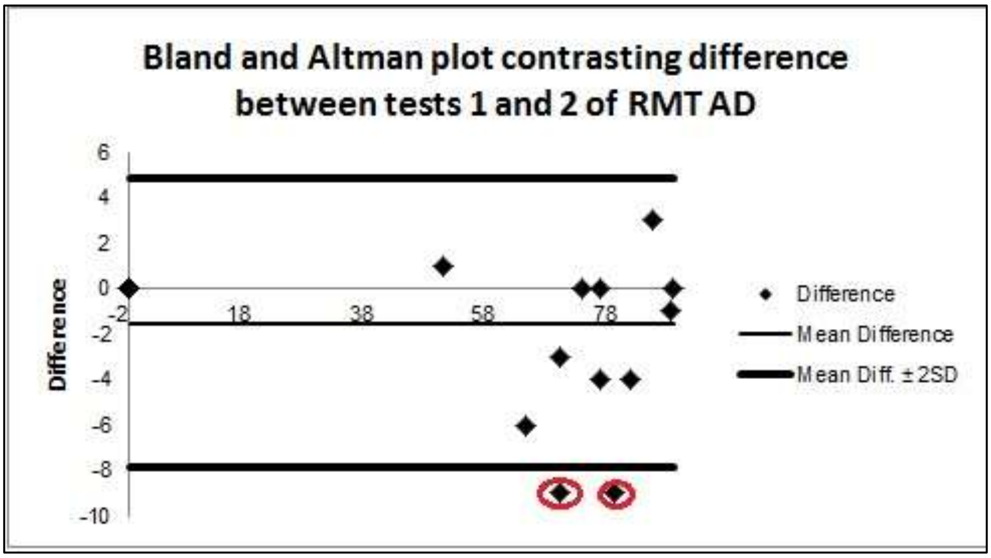

Figure 5.6 Plot of difference in anterior deltoid resting motor threshold between tests 1 and 2
(Red circle represents an outlier)

The data of the RMT between tests 1 and 3 are also presented on the right side of the Bland and Altman plot (Figure 5.7) i.e. the participants needed a lower intensity on test 3 compared to test 1.

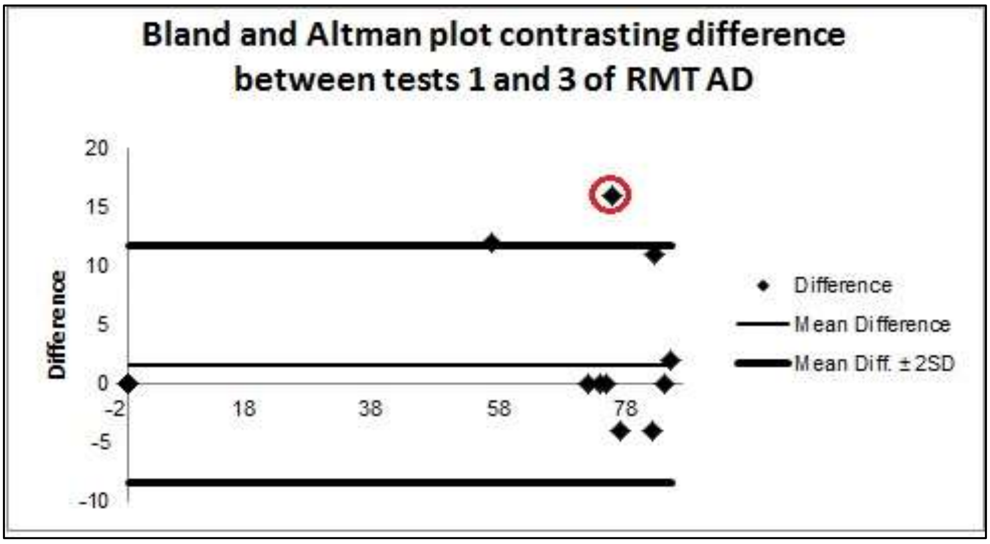

Figure 5.7 Plot of difference in anterior deltoid resting motor threshold between tests 1 and 3
(Red circle represents an outlier)

In summary, this section has demonstrated that the measurement of the RMT of AD and ED muscles between tests 1 and 2 and tests 1 and 3 showed strong level of agreement. The Bland and Altman plots showed a wider spread of data for the ED muscle than the data for the AD muscle.

5.9.2.2 Reliability of motor evoked potentialamplitude

Reliability analysis showed that the MEP amplitudes for the ED between Test 1 and 2 had a poor to moderate level of agreement with wide confidence intervals for intensities ranging from 100-150% of RMT (ICC=0.371-0.691). Between tests 1 and 3 moderate agreement at intensities 100%, 120-140% (ICC=0.509-0.730) and poor agreement for intensities 110% and 150% of RMT of ED was found (ICC=0.158-0.238) (Table 5.4).The MDC for ED MEP amplitude at 100% RMT was 98.76 (µV). The MDCs for ED MEP amplitude between 110-150% of RMT were found at 444.94 (µV), 527.18 (µV), 397.82 (µV), 703.28 (µV) and 919.59 (µV) respectively.

Table 5.4 Intra-class coefficients with confidence intervals of motor evoked potential means (extensor digitorum muscle) at 100-150% of RMT between tests 1-2 and tests 1-3

MEP Amplitude	Means (SD) (µV)	ICC[*1]	CI[*2]	SEM[*3]	MDC[*4]
Test 1 and 2 (100% ED)	120.80 (69.66) 115.79 (52.03)	0.416	0.008-0.713	46.49	**-**
Test 1 and 3 (100% ED)	120.80 (69.66) 117.85 (45.69)	0.614	0.246-0.827	35.63	**98.76**
Test 1 and 2 (110% ED)	281.23 (207.40) 298.81 (301.00)	-0.263	-0.416-0.429	175.55	**-**
Test 1 and 3 (110% ED)	281.23 (207.40) 236.63 (142.31)	0.158	-0.295-0.553	160.52	**444.94**
Test 1 and 2 (120% ED)	407.22 (331.19) 412.81 (345.02)	0.650	0.262-0.857	200.16	**-**
Test 1 and 3 (120% ED)	407.22 (331.19) 374.03 (268.78)	0.598	0.195-0.828	190.19	**527.18**
Test 1 and 2 (130% ED)	470.87 (255.77) 485.36 (361.02)	0.617	0.209-0.842	190.90	**-**
Test 1 and 3 (130% ED)[*5]	470.87 (255.77) 533.97 (296.67)	0.730	0.366-0.901	143.52	**397.82**
Test 1 and 2 (140% ED)[*6]	595.34 (313.16) 560.39 (399.05)	0.691	0.275-0.889	197.96	**-**
Test 1 and 3 (140% ED)[*6]	595.34 (313.16) 653.70 (410.96)	0.509	-0.007-0.811	253.70	**703.28**
Test 1 and 2 (150% ED)*[7]	599.40 (369.35) 604.58 (417.49)	0.553	-0.122-0.878	263.04	**-**
Test 1 and 3 (150% ED)[*8]	599.40 (369.35) 711.32 (390.69)	0.238	-0.392-0.716	331.76	**919.59**

[*1]ICC=Intraclass Coefficient, [*2] CI=Confidence Interval, [*3] SEM= Standard error of mean [*4] MDC= Minimal Detectable Change (measured between teat 1 and 3), [*5]Data of 19 participants, [*6] Data of 17 participants, [*7] Data of 12 participants, *[8] Data of 11 participants

A moderate to excellent level of agreement for MEP amplitudes was shown for the AD at 100-120% of RMT (ICC=0.527-0.903) with wide confidence intervals between tests 1 and 2. A poor level of agreement was found for 100% of RMT but a moderate to substantial agreement was found at 110% and 120% of RMT between tests 1 and 3 for the AD muscle (Table 5.5). The MDC for AD 100-120% intensity of RMT was found at 151.62 (µV), 111.40 (µV) and 412.67 (µV) increase in MEP amplitude respectively.

Table 5.5 Intra-class coefficients with confidence intervals of the motor evoked potential mean (AD muscle) at 100-150% of RMT between tests 1-2 and tests 1-3

MEP Amplitude	Means (SD) (µV)	ICC[*1]	CI[*2]	SEM[*3]	MDC[*4]
Test 1 and 2 (100% AD)	118.95 (90.51) 102.07 (72.81)	0.527	0.110-0.857	56.16	
Test 1 and 3 (100% AD)	118.95 (90.51) 91.17 (27.50)	0.140	-0.581-0.737	54.70	**151.62**
Test 1 and 2 (110% AD)[*5]	153.11 (85.35) 194.82 (158.38)	0.627	0.40-0.892	74.46	
Test 1 and 3 (110% AD)	153.11 (85.35) 161.20 (86.05)	0.780	0.236-0.952	40.19	**111.40**
Test 1 and 2 (120% AD)[*6]	296.55 (163.89) 294.29 (175.41)	0.903	0.343-0.989	52.76	
Test 1 and 3 (120% AD)	296.55 (163.89) 230.26 (267.013)	0.522	-0.502-0.937	148.88	**412.67**

[*1]ICC=Intraclass Coefficient, [*2] CI=Confidence Interval, [*3] SEM= Standard error of mean [*4] MDC= Minimal Detectable Change, [*5]Data of 11 participants, [*6] Data of 7 participants

The differences in MEP of ED muscle between tests 1 and 2 and tests 1 and 3 against the mean values for each participant are plotted in the following Bland and Altman plots as explained in the previous section. Six plots are presented in this chapter. The Bland Altman plots showed one outlier (outside the mean difference ± 2SD).

From the Bland and Altman plot of MEP amplitude of ED muscle between tests 1 and 2, the data are clustered to the left side of the plot however, there are equal positive and negative data points (Figure 5.8). It was noted that there was moderate agreement between MEP amplitude of the ED muscle between tests 1 and 3; data points were moderately spread however, there are more positive values above the mean difference showing that for test 2, the participants had lower MEP amplitudes (Figure 5.9).

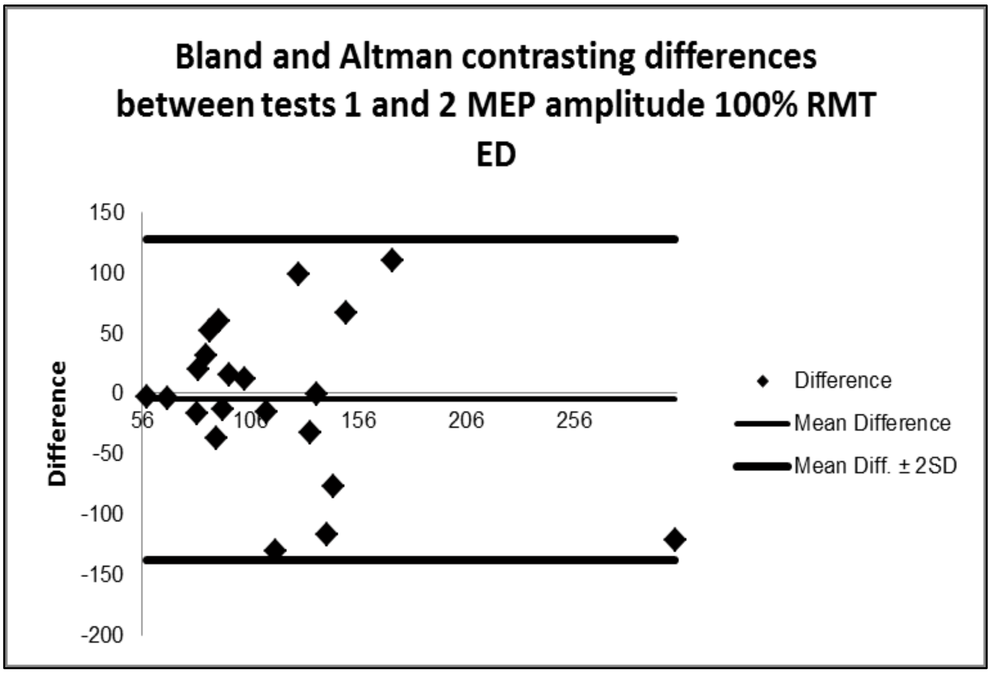

Figure 5.8 Plot of difference in extensor digitorum motor evoked potential at 100% of resting motor threshold between tests 1 and 2.

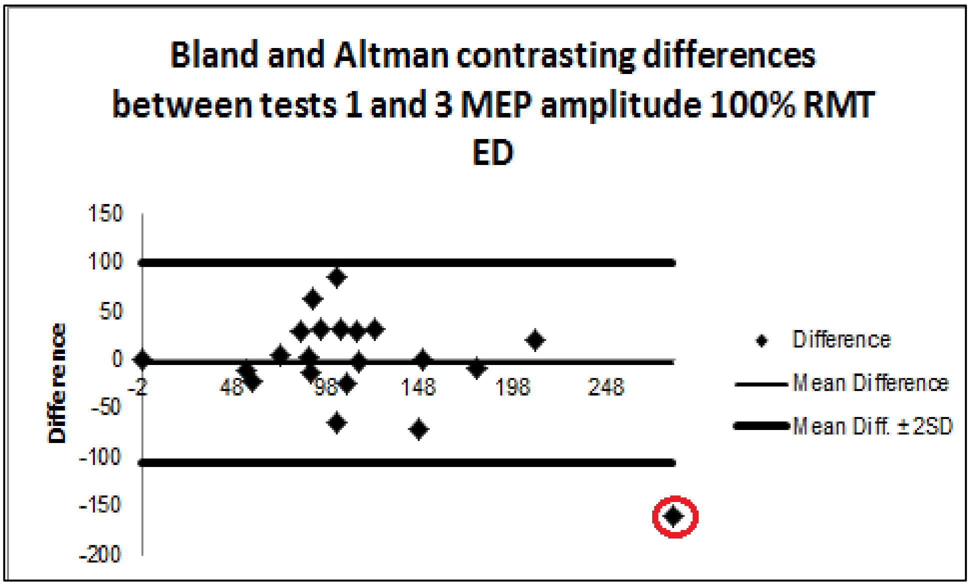

Figure 5.9 Plot of difference in extensor digitorummotor evoked potential at 100% of resting motor threshold between tests 1 and 3 (Red circle represents an outlier)

Similar plots were noted for the AD muscles at 100% TMS intensity between tests 1 and 2 and tests 1 and 3 (Figure 5.10 and Figure 5.11). There are more data points on the positive side of the mean difference indicating that lower MEP amplitudes were obtained at test 1 compared to test 2 and test 3 for the AD muscle at 100% of RMT.

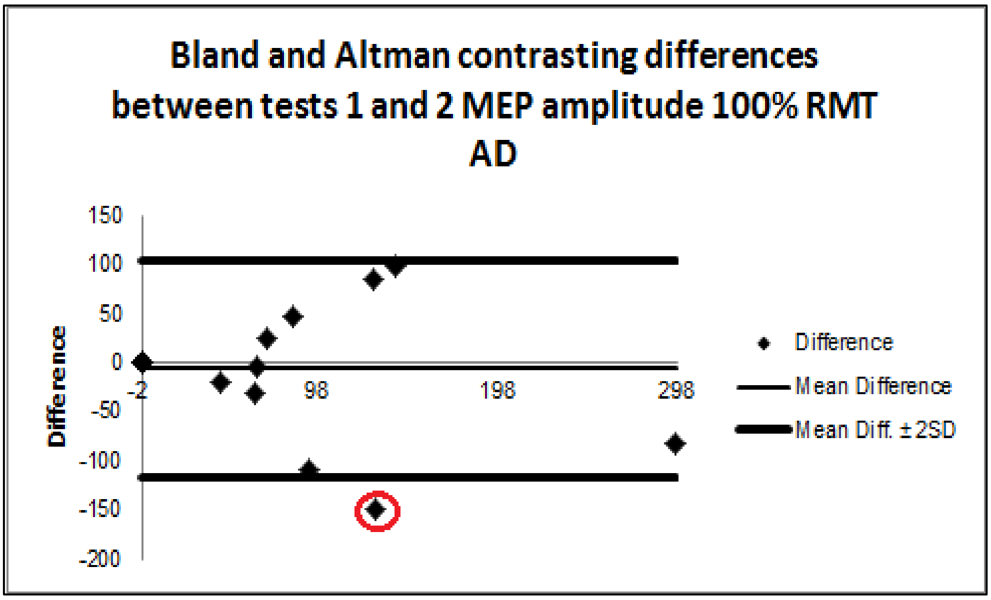

Figure 5.10 Plot of difference in anterior deltoid motor evoked potential at 100% of resting motor threshold between tests 1 and 2
(Red circle represents an outlier)

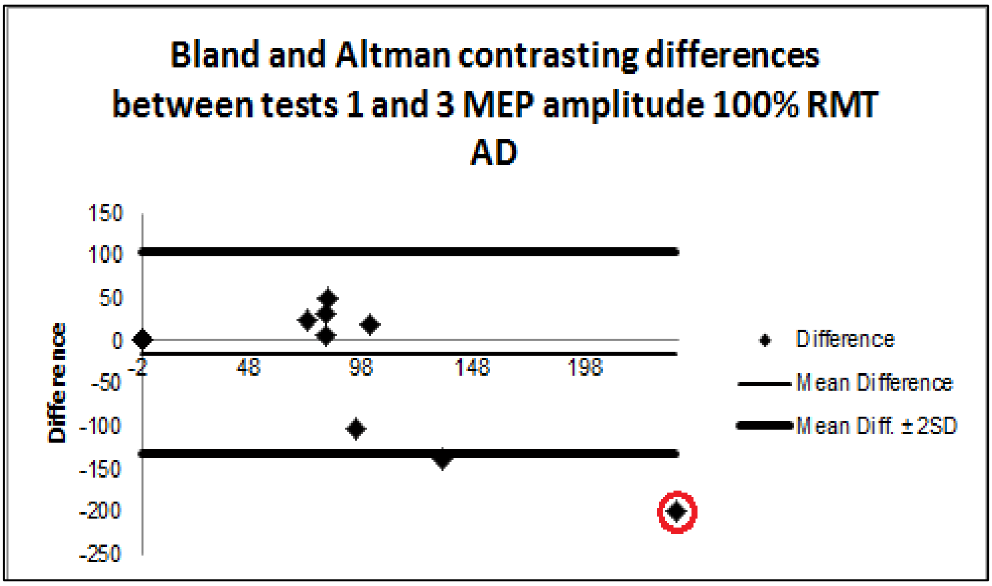

Figure 5.11 Plot of difference in anterior deltoid motor evoked potential at 100% of resting motor threshold between tests 1 and 3
(Red circle represents an outlier)

The remaining two plots presented in this chapter are for TMS percentages where a stronger agreement (ICC=0.730-0.780) was found for MEP amplitude of ED and AD. A substantial agreement was found at 130% of RMT between tests 1 and 3 (Figure 5.12). As noted from the Bland and Altman, the data is spread out evenly above and below the mean difference and there were no outliers. A substantial agreement was also found at 110% of RMT between test

1 and 3 (Figure 5.13). However, this plot shows a weaker level of agreement than the aforementioned plot of ED probably due to fewer responses from the AD muscle. The remaining plots are presented in Appendix H.4.

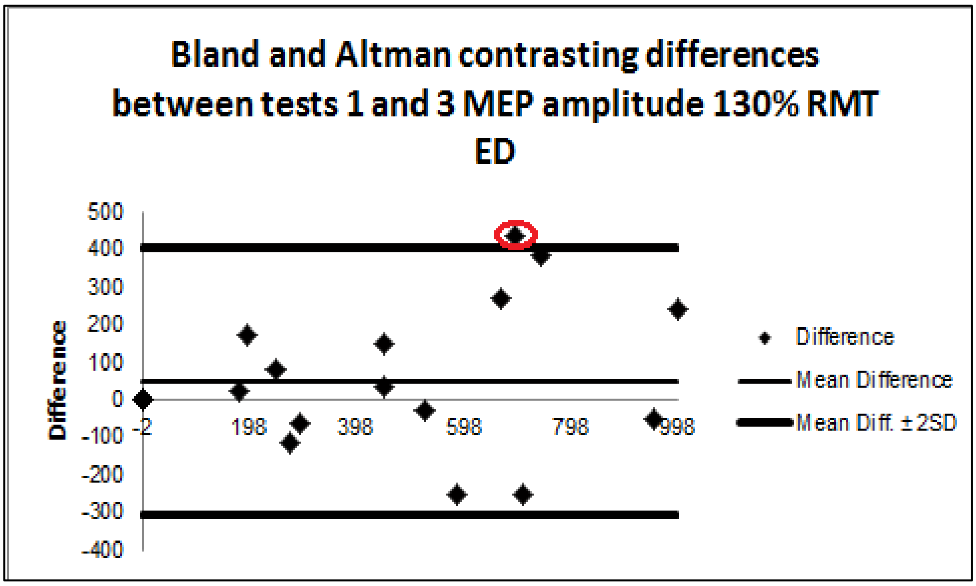

Figure 5.12 Plot of difference in extensor digitorum motor evoked potential at 130% of resting motor threshold between tests 1 and 3

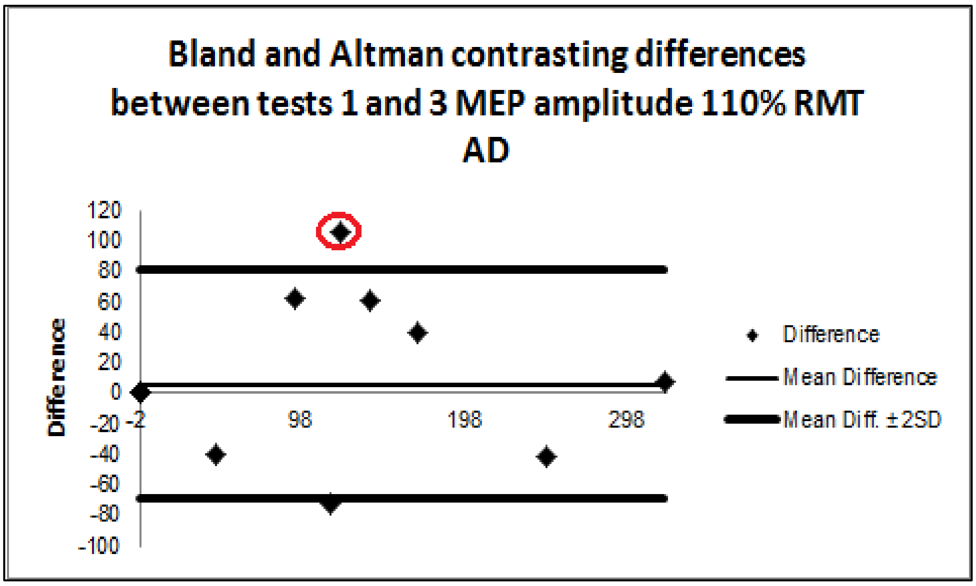

Figure 5.13 Plot of difference in anterior deltoid at 110% resting motor threshold between tests 1 and 3
(Red circle represents an outlier)

5.9.2.3 Comparison of reliability between the left and right groups

The data for the RMT ED was split in the left and right groups and the level of agreement was compared. Similarities were found between the left and right groups for levels of agreement (ICC=0.818-0.911) (Table 5.6) and MDC (11.92- and 11.34 % respectively).

Table 5.6 Difference between the intra-class coefficients with confidence intervals of the resting motor threshold of extensor digitorum muscle between the right and left groups between tests 1-2 and tests 1-3

RMT	Means (SD) (%)	ICC*1	CI*2	SEM*3	MDC4
Test 1 and 2 (Right group)	57.10 (10.34) 57.40 (11.11)	0.898	0.643-0.974	3.42	--
Test 1 and 2 (Left group)	59.82 (9.48) 60.91 (12.78)	0.911	0.705-0.975	3.32	--
Test 1 and 3 (Right group)*5	57.10 (10.34) 60.20 (9.81)	0.818	0.386-0.956	4.30	**11.92**
Test 1 and 3 (Left group)	59.82 (9.48) 60.36 (11.72)	0.851	0.539-0.958	4.09	**11.34**

*1ICC=Intraclass Coefficient, *2 CI=Confidence Interval, *3 SEM= Standard error of mean

The reliability of MEP amplitude at 100% of RMT was also analysed between the left and right groups. It was noticed that ICC levels were slightly higher i.e. stronger agreement in the right group (Table 5.7). The MDC for the Right group was 109.43 (µV) and the left group was 84.51 (µV).

Table 5.7 Difference between the intra-class coefficientswith confidence intervals of the motor evoked potential amplitude of extensor digitorum muscle at 100% of resting motor threshold between the right and left groups between tests 1-2 and tests 1-3

MEP Amplitude	Means (SD) (µV)	ICC*1	CI*2	SEM*3	MDC*4
100% Test 1 and 2 (Right group)	147.06 (87.39) 144.61(58.18)	0.372	-0.297-0.796	57.65	-
Test 1 and 2 (Left group)	96.92 (38.93) 89.60 (27.98)	-0.127	-0.655-0.485	16.93	-
100% Test 1 and 3 (Right group)*5	147.06 (87.39) 128.92 (51.76)	0.678	0.81-0.917	39.48	**109.43**
Test 1 and 3 (Left group)	96.92 (38.93) 108.78 (40.26)	0.407	-0.221-0.796	30.49	**84.51**

*1ICC=Intraclass Coefficient, *2 CI=Confidence Interval, *3 SEM= Standard error of mean, *4 MDC=Minimal Detectable Change

5.9.2.4 Differences in reliability between the young and older adults

As described in the data analysis (section 5.8) the data for the RMT ED was split in Young Adult (YA) (data of 10 participants) and Older Adult (OA) (data of

11 participants) groups and the level of agreement was compared. It was noticed that the OA had an excellent and stronger agreement (ICC=0.956) than the YA group which was moderate (ICC=0.549) for RMT of ED between tests 1 and 2 (Table 5.8). However between tests 1 and 3 the level of agreement was moderate (ICC=0.587 and 0.60) and similar between YA and OA. The MDC for RMT of the ED has a score of 9.15% in YA however a larger MDC score of 22.48% for OA.

Table 5.8 Difference between the intra-class coefficients with confidence intervals of the resting motor threshold (extensor digitorum muscle) between the young adult and older adult between tests 1-2 and tests 1-3

RMT	Means (SD) (µV)	ICC*1	CI*2	SEM*3	MDC*4
Test 1 and 2 (YA group)	59.80 (4.52) 59.50 (6.22)	0.549	-0.80-0.865	3.61	-
Test 1 and 2 (OA group)	57.36 (12.99) 59.00 (15.68)	0.956	0.847-0.988	3.01	-
Test 1 and 3 (YA group)	59.80 (4.52) 58.40 (5.74)	0.587	-0.024-0.878	3.30	**9.15**
Test 1 and 3 (OA group)	57.36 (12.99) 62.00 (12.76)	0.60	-0.562-0.639	8.11	**22.48**

*1ICC=Intraclass Coefficient, *2 CI=Confidence Interval, *3 SEM= Standard error of mean, *4 MDC=Minimal Detectable Change

The level of reliability of MEP amplitude at 100% of RMT was stronger and moderate in YA group (ICC=0.655 and 0.539) compared to the OA (ICC=-0.075 and 0.11) between tests 1 and 2 and tests 1 and 3 respectively. The MDC was similar in the YA and OA group: 132.44 (µV) of MEP amplitude in YA and 127.42 (µV) of MEP amplitude in OA between test 1 and 3.

Table 5.9 Difference between the intra-class coefficients s with confidence intervals of MEP amplitude at 100% of resting motor threshold (extensor digitorum muscle) between the young adult and older adult between tests 1-2 and tests 1-3

MEP Amplitude	Means (SD) (µV)	ICC*1	CI*2	SEM*3	MDC*4
Test 1 and 2 (YA group)	120.65 (91.91) 118.26 (53.16)	0.655	0.90-0.902	42.61	_
Test 1 and 2 (OA group)	120.93 (45.87) 113.55 (53.48)	-0.075	-0.624-0.524	51.50	_
Test 1 and 3 (YA group)	120.65 (91.91) 125.95 (48.83)	0.539	-0.093-0.862	47.78	**132.44**
Test 1 and 3 (OA group)	120.93 (45.87) 121.64 (51.74)	0.11	-0.595-0.609	46.04	**127.62**

*1ICC=Intraclass Coefficient, *2 CI=Confidence Interval, *3 SEM= Standard error of mean, *4 MDC=Minimal Detectable Change

5.10 Summary of results

In total, 20 participants completed the reliability study. From the data analysis the following results were found:

- MEPs of the ED were elicited in all the participants
- MEPs of the AD were only elicited in 11 participants
- RMT of ED and AD muscles had excellent intra-rater and test-re-test reliability in all the participants and the MDC value of RMT between tests 1 and 3 was 10.87% for the ED muscle and 13.14% for the AD muscle.
- Bland and Altman plots showed that data:
  - were evenly spread around the mean difference in ED
  - were not evenly spread between the positive and negative values of AD
- Reliability analysis showed that the MEP amplitudes for the ED between tests 1 and 2 had poor to moderate level of agreement with wide confidence intervals for intensities ranging from 100-150% TMS intensity Between tests 1 and 3 moderate agreement at intensities 100%, 120-140 and poor agreement for 110% and 150% TMS intensities for ED was found. The MDC for ED MEP amplitude 100% TMS intensity was found at 98.76 (µV). The MDC for ED muscle was higher for 110-150% TMS intensities ranging from 397.82 (µV) - 919.59 (µV).

- Reliability analysis showed that the MEP amplitudes for the AD had moderate to excellent level of agreement for MEP amplitudes at TMS intensities 100-120% (ICC=0.527-0.903) however with wide confidence intervals between tests 1 and 2. A poor level of agreement was found for 100% TMS intensity but moderate to substantial agreement was found at TMS intensities 110% and 120% between tests 1 and test 3 for the AD muscle. The MDC for AD MEP amplitude at 100-120% TMS intensities was found at 151.62 (µV), 111.40 (µV) and 412.67 (µV) increase in MEP amplitude respectively.
- Bland and Altman plots showed less spread of data for MEP amplitude compared to RMT which represented the moderate to poor level of agreement between tests
- No differences in reliability were found between the left and right groups.
- OA group had an excellent and stronger agreement (ICC=0.956) compared to the YA group which was moderate (ICC=0.549) for RMT of ED between tests 1 and 2. Between tests 1 and 3 the level of agreement was moderate (ICC=0.587 and 0.60) and similar between YA and OA. The MDC for RMT of the ED has a score of 9.15% in YA however a larger MDC score of 22.48% for OA. The level of reliability of MEP amplitude at 100% TMS intensity was stronger and moderate in YA group compared to the OA which was poor between tests. The MDC was similar between both groups of 132.44 (µV) of MEP amplitude in YA and 127.42 (µV) of MEP amplitude in OA. (µV).

5.11 Discussion

In the present study, single pulse TMS was used to explore the effect of the intervention on the cortical excitability in stroke. To assess changes in cortical excitability, the RMT and the MEP amplitudes were measured. Generally, the AD needed a higher intensity in order to evoke a MEP response with amplitude of 50 (µV). MEPs of the ED were elicited in all the participants, but only elicited in eleven participants for AD. Eliciting distal muscles require less stimulus intensities due to the large representation of the hand in the motor cortex (Groppa et al., 2012).

This was the first study to measure the minimal detectable change value of RMT and MEP amplitude of the AD muscle. This reliability study also showed that the RMT at ED and AD muscles had excellent intra-rater and test-re-test reliability in all the participants. However, this study involved a small sample and therefore, further research is needed to explore reliability of this measurement including people with stroke. Reliability analysis showed that the measurement of MEP amplitudes for the AD showed moderate to excellent level of agreement at 100-120% of RMT (ICC=0.527-0.903), however with wide confidence intervals between tests 1 and 2.

A poor level of agreement was found at 100% of RMT, a moderate to substantial agreement was found at intensities 110% and 120% of RMT between tests1 and 3 of the AD muscle. Reliability analysis showed that the MEP amplitudes for the ED between tests 1 and 2 also had poor to moderate level of agreement with wider confidence intervals for percentage intensities ranging from 100-150% of RMT. This demonstrated that measurement of MEP amplitude of AD muscle is difficult but also variable on separate days if a different muscle such as the ED is used.

Between tests 1 and 2 of RMT measurement, a stronger level of agreement was found for the OA group compared to the YA group. Nerve accommodation from of the TMS single-pulse on the same day could have been the reason for the YA group needing a higher TMS intensity to elicit a 50(µV) MEP response during the second measurement.

Measurement of RMT of the ED muscle could potentially be a reliable tool for neurological rehabilitation trials. However, further research is required exploring its inter-rater reliability with people with stroke.

5.12 Conclusion

This chapter presented a reliability study of the assessment of MEP response-RMT and MEP amplitude in healthy adults. It was found that measurement of RMT of the ED and AD muscles showed excellent intra-rater and test-retest reliability. Measurement of MEP amplitude showed poor to moderate intra-rater and test-retest reliability. The results found in this study and the related limitations will be discussed and compared to similar studies in detail in section 6.6.2 of the next chapter.

Chapter 6

Discussion

6.1 Introduction

This thesis has presented a systematic review with meta-analyses followed by a pilot double-blinded randomised controlled trial (RCT) exploring the combination of robot therapy (RT) with transcranial Direct Current Stimulation (tDCS) for the impaired upper limb (UL) in stroke. In addition, a reliability study of the cortical excitability measurement involving healthy participants has also been presented as an important basis for the RCT.

The main objectives of this research were to: a) explore the effectiveness of multiple sessions of tDCS and rehabilitation on UL recovery following stroke and b) examine the feasibility of the intervention (RT and tDCS) and c) through the pilot RCT, to test the potential clinical benefits of the combination of RT and tDCS in stroke and inform the design of a larger clinical trial. In this chapter, the feasibility component and the findings obtained from the conducted research are discussed. This involves the examination of each component, RT in addition with real or sham tDCS. This is followed by a reflection of the use of tDCS as an intervention in stroke rehabilitation and an evaluation of current assessments in the context-relevant, recent research. Finally, the limitations of the research are discussed followed by a conclusion of the discussion.

6.2 Feasibility component of the pilot randomised controlled trial

Feasibility was examined in terms of: the recruitment process and criteria, assessment and intervention protocol, adverse reactions to tDCS and RT, the practicality of the intervention and time and resources needed to carry out the research (Arain et al., 2010). These issues are discussed based on the views and perceptions of all the participants that took part in the trial in the next sub-sections.

6.2.1 Recruitment process and criteria

Four changes were made to the recruitment protocol. The research nurses and clinicians identified potential participants for the study. Eligible individuals with stroke were then approached and if they showed interest, were provided with an information pack. On receipt of the reply slip, the main researcher, (LTT), contacted the potential participant and an appointment at the Laboratory at the University was arranged. Following the experience of one participant this part of the recruitment process was amended. The participant concerned became anxious on arrival at the lab when she saw the Transcranial Magnetic Stimulation (TMS) and BrainSight® equipment and consequently decided not to take part in the study. Clearly the 'hi-tech' equipment in the lab can be daunting for some participants. Therefore, the first amendment made to the recruitment protocol was that before the participant attended the first session at the University, the researcher (LTT) visited participants at their own home to discuss the study, answer any questions they might have and showed them a video as part of the participant information pack which had a positive outcome. This provided an opportunity for them to meet the main researcher in a familiar environment.

Evidence shows that from all potential stroke participants, 30% were above 80 years old and 23% had a previous stroke (Di Carlo et al., 1999, Kammersgaard et al., 2004). These participants were excluded from the trial and therefore impacted on the recruitment rate. The research team discussed changing the criteria to the inclusion of people with multiple strokes for the pilot RCT in order to improve recruitment. However, in order to eliminate additional confounding factors and as most of the studies exploring similar research questions to this present study also included people with only one stroke, it was decided not to change the criteria (Hesse et al., 2007, Hesse et al., 2011). This ensured that the final results would be comparable to other studies. However, there was insufficient evidence justifying the exclusion of participants over 80 years old. Therefore, recruiting participants over 80 years old was the second amendment to the recruitment protocol.

Recruiting participants with sub-acute stroke was slower than expected, despite support from the research nurses and clinicians at each NHS site. Therefore, a contingency plan was discussed by the research team and this in fact increased the recruitment rate (Figure 6.1). Recruitment from non-NHS sites was initialised after ethical amendment was sought. Additionally, an advert was published in a local newspaper, 'The Daily Echo', to increase recruitment rate however, nearly all of the participants who contacted the researchers did not meet the eligibility criteria (Appendix B.1.5).

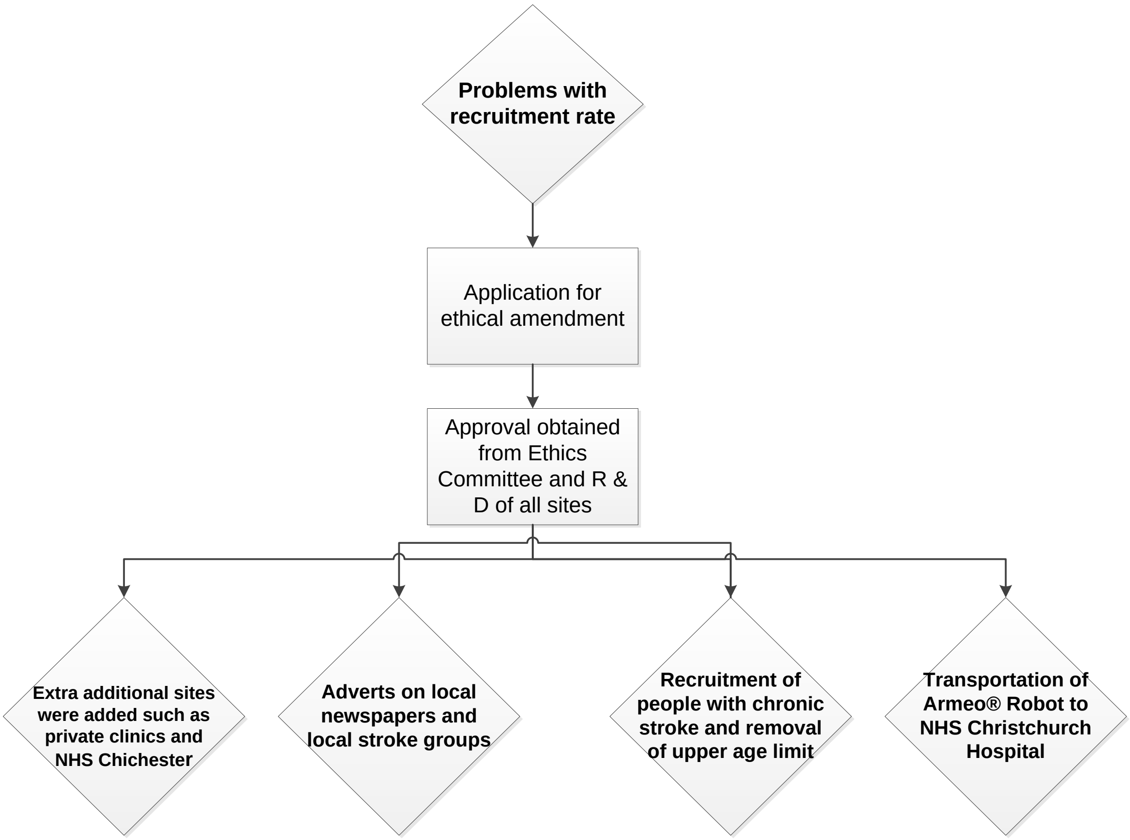

Figure 6.1 Contingency plan to increase the recruitment rate

Travelling to the University from more remote places (e.g. Bournemouth) was also potentially affecting the recruitment rate. The first six participants recruited were asked about issues relating to taking part in the study during the post intervention interviews. Some stated that travelling was an issue due to the time involved and lack of transport. To mitigate this potential impact, an additional Armeo®Spring Robot was therefore transported to the NHS Christchurch Day Hospital. Since most of the recruited participants came from this area, hence the chosen location. As a result, the participants interviewed after this process did not report any difficulties with travel. Therefore, this was the third amendment to the protocol.

After, nine months of recruitment, only eight participants with sub-acute stroke were recruited even though an additional NHS Trust was added. The team discussed the small sample and the slow recruitment rate. Therefore, the final amendment to the protocol involved recruiting participants with chronic stroke to the trial. Recruiting people with chronic was quicker and easier.

People in the sub-acute stage were in the peak-time for natural and motor recovery (O'Dell et al., 2009, Langhorne et al., 2011). However, UL improvements have also been reported after both RT and tDCS involving people with chronic stroke (Lo et al., 2010, Bolognini et al., 2011). Therefore, including both groups allowed comparison of the effect of the intervention on UL impairments and function of people with sub-acute and chronic stroke.

6.2.2 Assessment and intervention protocol for the study

To ensure patient comfort, minor changes were made to the original protocol based on the experiences of the first six participants. The initial protocol for the screening and assessment procedure lasted longer than expected. It was anticipated that the first assessment would last two hours. However, on three occasions it lasted between two and three hours. The neurophysiological assessment involving Transcranial Magnetic Stimulation (TMS) took the most time since two recruitment curves of two different muscles were measured. However, as this was critical for the study it was not reduced, but regular breaks (with refreshments) were provided for the participants and carers.

Due to an increase in synaptic activation in the brain and spinal cord, measuring active motor threshold results in a larger Motor Evoked Potential (MEP) response than Resting Motor Threshold (RMT) when the muscle is relaxed (Ridding and Rothwell, 2007). Measurement of the active motor threshold required the participant to activate the muscle (e.g. flexing the shoulder) for a prolonged period, which for the first participant resulted in fatigue. Therefore, this was removed for the assessment list. This reduced the assessment time by 20 minutes and avoided having to spread the assessment over two days. However, participants did express their view that the assessment session was tiring during the interview. Future research should look into reducing non-essential outcome measures such as the Hospital Anxiety and Depression Scale (HAD).

6.2.2.1 Deviation from protocol

There was one deviation from the intervention protocol. Two participants were only able to attend two treatment sessions per week because they found visiting the laboratory tiring. Therefore the intervention was spread over ten weeks rather than eight. Some people with sub-acute stroke were still in the stage of-adjustment and feel 'passive' since they need to depend on their families or health care professionals to carry out activities (Wottrich et al., 2012, Satink et al., 2013). The extension of the programme from eight to ten weeks was considered by the research team. However, the team decided against, in order to maintain the intensity of the intervention. Intensity is an important factor that drives motor recovery and neuroplasticity (Biernaskie et al., 2005, Kwakkel et al., 2004a). Minor deviations to the planned intervention occurred due to technical issues during the 18 sessions. Potentiometers and cables within the Armeo® required replacing. As replacements had to be ordered from Switzerland, this sometimes delayed the intervention sessions by three days, which caused frustration by some of the participants. This disruption to the research process highlighted the need for close technical support when integrating such technology within clinical practice. The feasibility issues regarding the assessment and intervention process have just been discussed with the exception of adverse reactions that are discussed in the next section.

6.2.2.2 Adverse reactions from non-invasive brain stimulation and robot therapy

The TMS assessment was a potential concern since there is a low risk of a seizure (1%) following the application of TMS (Rossi et al., 2009). However, in this study TMS did not cause any adverse reactions. Participants receiving real tDCS did report sensations and these can be compared to 117 tDCS studies have reported such sensations (Brunoni et al., 2011). From the Table 6.1, it is noted that the percentages are lower than the ones found in this study.

Table 6.1 Reported sensations in the present study compared to other published studies

Reported sensation	Percentage in the present study	Percentage found in published tDCS studies (Brunoni et al., 2011)
Tingling	58	22
Itching	58	39
Burning	50	9
Headaches	8	15

Burning sensations were reported by 9% of the participants receiving tDCS in the published studies. The latter percentage is lower than 50% reported in the present study. Potential limitations could be that the current reporting tools of tDCS are not of high standard. Moreover, prolonged immersion of the sponge pads in the saline solution (instead of completely drying them off before stimulation) caused less impedance and decreased sensations for some of the participants who previously reported the aforementioned adverse reactions.

However, with bald participants immersing the sponges in saline solution increased the sensations of burning and warmth. The bald participant who experienced a first degree burn under the anode electrode also had hypersensitive skin. Adverse reactions such as skin burns have been reported in a few cases receiving real tDCS (Palm et al., 2008). Skin impedance is dependent on the stimulation time, current intensity and density, however, it is highly variable across subjects (Prausnitz, 1996, Hahn et al., 2012). The tDCS equipment used for the present study did not display the impedance level of the direct current moving across the body and the electrodes. A sudden drop in impedance may potentially cause a surge in the current (Hahn et al., 2012). The voltage applied in order to ramp up the current (1mA) depends on this impedance. Recently, research has been carried out in order to decrease the voltage which allows enough time for the impedance to decrease (Hahn et al., 2012).

With regard to the whole intervention including RT, 55% of the sample of the present study reported fatigue. Fatigue is commonly experienced by individuals with stroke (29.2%) and carrying out an intensive intervention such as RT can increase it (Glader et al., 2002, Mead et al., 2011). Adverse events are rarely reported after RT in stroke (Mehrholz et al., 2012). A recent study using a similar robot (ArMIN) to the one used in the present study did report that RT caused bruising in two participants (Klamroth-Marganska et al., 2013). Participants from the present study reported pain at the shoulder of the affected UL and upper trapezius muscle of unaffected side. Shoulder pain on the affected side is common after stroke and it is reported in around 5 to 84% by people with stroke (McKenna, 2001, Turner-Stokes and Jackson, 2002). Participants did not feel an increase in pain levels after the sessions and similar research reported insignificant differences in pain levels after RT (Lo et al., 2010). However, participants did report pain at the unaffected shoulder and trapezius after some of the sessions and this could have been contributed to compensatory movements of the unaffected side whilst moving the affected arm which is common in stroke (Kwakkel, 2006).

6.2.3 Project resources

A total of 446 sessions (including all intervention and assessments) were carried out for the twenty-three participants. In view of the fact most of these sessions were mainly carried out by one person (LTT), around 900 hours were spent by the researcher to ensure that the sessions would run smoothly. Assistance from the clinical assessors during the assessments and an additional researcher during the intervention sessions carried out between June and July of 2013 was found very beneficial. Future trials should consider how time could be better used and resources better managed by also employing research assistants to the project.

One expense of running the trial was the re-imbursement of the participants' travels to and from the lab. Most of the participants were recruited outside Southampton and, therefore travel costs were very high especially when considering an intervention that lasted for 21 sessions. Funding obtained from Malta and the European Union subsidised bench fees and travel expenses for the participants and therefore, the travel and recruitment of participants from sites outside Southampton was only feasible with extra funding. This expense could be minimised if the intervention was carried out at the participants' home involving a smaller robot.

Therefore, a future study involving tDCS and RT will be adapted and planned based on the aforementioned feasibility issues discussed:

- Recruitment of participants with sub-acute and chronic stroke will be involved
- The criteria will not include an upper age limit
- Better technical support for RT at the research site will be needed
- Purchase of a tDCS stimulator equipment with impedance monitor
- Reduction of outcome measures
- Extra funding for research assistants to deliver the intervention
- Consideration of home-based rehabilitation needs to be addressed

These factors will be discussed in the next chapter focussing on future work. The next section discusses the clinical findings from the present RCT.

6.3 Summary of findings from pilot randomised controlled trial

Twenty-two participants (twelve sub-acute and ten chronic) completed the trial, and all participants continued their concomitant treatment during the trial and follow-up. Involving two groups (sub-acute and chronic) provided further information about the use of RT and Non-Invasive Brain Stimulation (NIBS) in different stages of stroke. Twelve participants who completed the RCT were in the sub-acute phase and, therefore, natural recovery was also occurring at the same time. The design of the present study does not allow one to distinguish the changes excluding natural recovery for participants in the sub-acute stage. The research question for the present study addressed whether adding tDCS enhances recovery over and above natural recovery, standard therapy and RT. Any changes noted in the chronic group were potentially due to the intervention and their concomitant treatment for the UL.

Twenty participants showed an improvement in UL impairments at post-intervention and three-month follow-up. A significant improvement in UL impairments was found at post-intervention and three-month follow-up in relation to the baseline in the sub-acute group. The chronic group only showed a significant improvement in UL impairments at post-intervention. It was shown that a sub-cortical stroke was an important predictor for the improvement in UL motor impairments. No significant values were found between the real and sham groups however, there was a positive trend towards the real group on UL impairment. Only participants with sub-acute stroke showed a significant improvement in the UL function, dexterity and activities. A significant reduction in stroke impact was found for the real sub-acute group but non-significant for the sham group at post-intervention for the sub-acute group. Significant reduction in stroke impact was found for both the real and sham groups at follow-up of the sub-acute group. Non-significant differences were found at post-intervention however, significant differences were found at follow-up for the chronic (real and sham) groups. No significant changes were found in the spasticity, depression and anxiety scores for the sub-acute group however a significant increase in spasticity at the wrist flexors was found for the chronic group at the follow-up assessment. Problems were encountered during the neurophysiological data collection and analysis. A high TMS intensity was needed to elicit a MEP of the extensor digitorum and therefore, data of five sub-acute participants was analysed. The cortical excitability data was therefore difficult to interpret. From the first and last robot session, participants showed a significant decrease in Hand Path Ratio (HPR) and therefore presented with improved co-ordination after the intervention. These results are discussed in the next sections.

6.4 The effect of the intervention on upper limb impairments, function, activities and stroke impact

In the literature,the percentage of UL recovery in stroke varies widely. At six months post-stroke, 33% to 66% do not present with recovery of UL function and only 5-20% achieve full recovery (Kwakkel et al., 2003, Kwakkel and Kollen, 2013). People with stroke experience difficulties using their arm even four years after their stroke (Broeks et al., 1999). Stroke is a catastrophic event which affects various aspects of that person’s life (Ellis-Hill et al., 2008). Not only does it cause obstacles during Activities of Daily Living (ADLs) but it also affects the quality of life of individuals with stroke (Nichols-Larsen et al., 2005). Thus, the current research drive is to promote new technologies such as RT and NIBS for the UL during all stages of stroke recovery. A discussion is now presented about the effect of intervention of the present study in sub-acute and chronic stroke followed by the augmentation of real versus sham tDCS in addition with RT on the UL in stroke.

6.4.1 The effect of the intervention on upper limb motor recovery, activities and stroke impact in sub-acute and chronic stroke

In the present RCT, the results showed that at post-intervention a significant decrease in UL impairments of people with acute and chronic stroke was reported after 18 sessions of RT and tDCS.

Improvement in rehabilitation is associated with the amount of training and also depends on the task being practiced repetitively (Krakauer, 2006). This is influenced by the learning process that takes place during the task. Motor skill learning occurs through the process of restitution of any premorbid movement patterns and adaptation of the remaining motor movements by either substitution and compensation (Levin et al., 2009). In the present study, a minimal clinically important difference (10 points on FMA) in UL impairments of people in the sub-acute stage (refer to Table 4.7 on page 141) (Gladstone et al., 2002). Early improvement was expected in the participants in the sub-acute group due to spontaneous natural recovery involving surrounding areas to the lesion (restitution) (O'Dell et al., 2009). In the first few hours and weeks after a stroke, natural recovery involves a decrease in local oedema and resolution of diaschisis of areas of metabolically depressed cortical tissue (Teasell et al., 2005). Recovery also involves reorganisation of the brain tissue and learning and this occurs during the first six months post-stroke (Langhorne et al., 2011, O'Dell et al., 2009). Due to greater neuroplastic changes, motor recovery and learning occurs mainly in the first three months after a stroke involving substitution and compensation (Jørgensen et al., 1995, Ward, 2005, Kwakkel et al., 2006, O'Dell et al., 2009, Langhorne et al., 2011). In animals it was shown that there is a limited time of up to eight weeks for molecular, physiological and cellular cortical changes to occur post-stroke (Winship and Murphy, 2008, Murphy and Corbett, 2009). However, these studies only measured short-term rather than long-term effects.

RT is not commonly used with people with acute or sub-acute stroke with UL impairments (Masiero et al., 2007, Burgar et al., 2011, Masiero et al., 2011). Studies involving this population show that RT is beneficial but it still does not show any significant differences compared to intensive therapy/exercise programmes. Participants receiving RT presented with similar improvements in their UL to the control group receiving conventional therapy (at least 25 hours, 4-5 hours a week for 5 weeks) (Masiero et al., 2011). Intensive movements have been associated in increased synaptic connections in the motor cortex of animals (Luke et al., 2004b, Kleim et al., 2002). However, traditional therapy programmes carried out in research are not a true representation of the conventional therapy provided in normal clinical stroke practice. In most countries, people with stroke do not receive high intensive therapy for the UL during the acute and sub-acute setting. The prime aim during the period is mobilisation and promotion of functional lower limb activities (West and Bernhardt, 2013). Thus, people with stroke present with long-term UL problems in the chronic phase.

A six point change on FMA is a clinically significant UL impairment improvement in people with chronic stroke (Page et al., 2012). For the chronic group in the present study, the intervention was the main factor that influenced the improvement since natural recovery could potentially be excluded. Therefore even at years' post-stroke, UL improvements can still occur which might not be a result of true motor recovery but of compensatory movements (Levin et al., 2009). As a result, recovery might not reach a plateau after six months (Demain et al., 2006, Klamroth-Marganska et al., 2013). At follow-up, participants with sub-acute stroke maintained the changes in UL motor impairments however, participants with chronic stroke showed a four percent decrease in the gain of movements achieved at post-intervention. People with chronic stroke require continual intensive therapy even after several years post-stroke. However, the current total stroke care cost is around nine billion per year and providing such long-term service can potentially increase the total cost (Saka et al., 2009). Integrating RT in community hospitals during the sub-acute stage might prevent severe UL impairments in the chronic stage and evidence shows that group RT can lead to lower overall healthcare costs than traditional rehabilitation (Wagner et al., 2011, Hesse et al., 2014).

Various researchers have explored the effect of RT in people with chronic stroke (Lo et al., 2010, Conroy et al., 2011, Hsieh et al., 2011, Liao et al., 2012). They all showed that high intensive RT leads to UL impairment improvements. However, when compared to a conventional intensive therapy for the UL no significant differences were found. In the present study, improvements in UL impairments were noted in the chronic group at post-intervention. A similar study compared conventional therapy to three-dimensional RT (ArMIN) with 77 people with chronic stroke. Significant differences were found in UL impairments in the robot group (Klamroth-Marganska et al., 2013). They also noted that participants with severe UL impairments significantly improved compared to the control group. Although a smaller sample size was involved in the present study, the noticed UL improvements were probably due to the type of RT. It has been recommended, that interventions such as RT should be provided daily for people with severe UL impairments. Therefore, participants might have shown a larger improvement if this was the case in the present study (Daly et al., 2005). No follow-up data were measured in the study by Klamroth-Marganska et al. and in fact, it is rarely reported in robot studies (Lo et al., 2010).

The lack of intensive therapy in current clinical practice results in around half of the people experiencing UL problems do not use their arm functionally after six months post-stroke (Kwakkel et al., 2003). In addition to measurement of impairments, it was also important to measure UL function using the Action Research Arm Test (ARAT). At post-intervention of this present study, it was noticed that participants with sub-acute stroke improved by 15.5% in UL motor function and dexterity and changes were maintained at follow-up. At post-intervention and follow-up, participants with chronic stroke only showed a 4% change in UL function and hand dexterity (refer to Table 4.10 on page 145). This could be attributed to increased compensatory activity of the upper arm which might result in prevention of the hand from gaining more control within the brain hand territory of the motor cortex (Muellbacher et al., 2002). One of the main problems experienced by people with stroke is hand function. In order to grasp and release, the hand needs to open, position, grip the object and then release that object (Connelly et al., 2010). People with stroke often have difficulty releasing the grip and extending the fingers due to a flexor synergy (Lodha et al., 2012). The lack of movement and activities involving the hand can result in increased tone which as a result, participants with chronic stroke presented with a significant increase in angle of catch at the follow-up assessment.

The Armeo®Spring robot and other exoskeletons have been shown to improve global UL movements but not hand dexterity (Lambercy et al., 2007). Robot studies involving dexterity measures do not report any significant differences in UL dexterity when compared to standard intensive programmes exercise (Lo et al., 2010). This was also discussed by the participants during the qualitative interviews of the present study. Hand modules for RT are currently being designed with a hand module to enhance hand dexterity and overall grasp release (Schabowsky et al., 2010, Godfrey et al., 2013). The lack of improvement at the hand has a significant impact on ADLs and a large impact on people experiencing a stroke.

In spite of this, the present study showed a significant effect of the intervention at post-intervention and at follow-up on UL ADLs (measured by Motor Activity Log) in the sub-acute group but not in the chronic group (refer to Table 4.15 on page 152). This was probably due to fewer participants experiencing severe UL impairments in the sub-acute group which was also raised during the interviews (Kwakkel et al., 2003). Nonetheless, in a recent Cochrane review it was reported that RT improves ADLs in the sub-acute phase but not in the chronic phase (Mehrholz et al., 2012). In addition, a non-significant small effect of tDCS on ADLs was found in the meta-analysis presented in chapter three and in another similar review (Elsner et al., 2013).

A significant improvement in stoke impact for participants in the sub-acute group but not in the chronic group at post-intervention (refer to Table 4.16 on page 153). Measuring stroke impact is important as part of the WHO's classification of disability (WHO, 2001). None of the previous studies involving tDCS have explored stroke impact and participation after the applied interventions. Participation is related to autonomy, quality of life and also depends on the environment of that person (Salter et al., 2005). Opportunities of choice, social responsibilities and interaction, control and have been shown to be prerequisites of participation (Hammel et al., 2008). In stroke, prerequisites of participation usually involve the reintegration in the social community and perception of stroke recovery and these are measured by using the Stroke Impact Scale (Eriksson et al., 2013). RT has been shown to significantly increase social participation compared to usual care (Lo et al., 2010). One important finding of the present study was that the chronic group showed a significant decrease in stroke impact at the three-month follow-up assessment. The reason behind this is that most of the participants stated that they increased their physiotherapy and rehabilitation sessions after the trial.

Therefore, one can speculate that the intervention of the present study improved UL impairments, activities and stroke impact in people with sub-acute stroke. They showed a larger improvement than the chronic group which could be attributed to natural spontaneous recovery, an ideal time for motor recovery, different tone and severity of UL impairment and different adjustment phase compared to the chronic group.

6.4.2 Augmenting tDCS with RT

No significant differences were found between the real tDCS and sham tDCS group. However, an overall significant effect of improvement was found. Focusing on the effect of RT on UL impairments in depth is necessary since both groups (real and sham) received RT.

6.4.2.1 The effect of RT on UL motor recovery

Conventional approaches targeting UL impairment have shown limited effectiveness (Van Peppen et al., 2004). As a result, technologies such as RT for UL impairment are becoming increasingly more popular (Lo et al., 2010, Dipietro et al., 2012).

A recent Cochrane review showed that RT can improve arm function and activities however, not specifically muscle strength (Merholz et al. 2012). They stated that the driver for recovery is probably the intensity, amount and frequency that any therapist can provide. However, this is debatable (French

2007, Lo et al., 2010, Norouzi-Gheidari et al., 2012). RT such as the Armeo®Spring enhances highly complex, intensive and repetitive movements and levels of motivation through feedback (Guidali et al., 2011). This extrinsic feedback is beneficial for implicit learning and thus UL motor recovery (Subramanian et al., 2010).

These factors could have been the contributors to both real and sham groups improving in UL impairments since both groups received RT. Using this type of robot allows people with stroke to play games in a virtual environment which is not usually carried out in clinical practice. Robots are an excellent source of measuring therapeutic efficacy through kinematic measures (Krakauer, 2006). In the present RCT, these measures were a beneficial source of monitoring improvement between sessions. Robot assessments provide an objective, quantitative approach to neurologically assess impairments. The use of such technology has provided a stepping stone towards accurately quantifying neurological impairment following stroke and reducing the time to assess such impairments (Scott and Dukelow, 2011). However, further research is needed in order to relate the information obtained from robot kinematic measures to ADLs in stroke rehabilitation. The next section involves a discussion exploring the effect of combining tDCS with RT for the impaired UL in stroke.

6.4.2.2 Real versus sham transcranial direct current stimulation and robot therapy for upper limb impairments, function and activities

From the meta-analyses described and discussed in chapter three, it was noted that there is a lack of research exploring the effect of multiple sessions of tDCS with rehabilitation techniques for the UL in stroke. From the seven papers reviewed, different tDCS regimes in addition with rehabilitation had a small but non-significant effect size on UL impairment and activity after stroke.

The null hypothesis was accepted for the present study, whereby adding on real tDCS did not result in significant differences compared to sham tDCS. A similar study explored the effects of RT and anodal, cathodal and sham tDCS in 96 participants with sub-acute stroke (Hesse et al., 2011). Even though the latter study involved a larger sample, non-significant differences were also reported between anodal, cathodal and sham on UL impairments. Similar to the present study, the anodal group improved by 11 points on FMA however, the participants were severely impaired at baseline. In the study by Hesse et al. (2011), the Bi-Manu Track® robot which is different to the Armeo®Spring (different types of robot were described in section 2.4.1 on page 30) was used. The Bi-Manu Track® only promotes bi-lateral wrist movements. Therefore, such an intervention does not promote movements of the shoulder, elbow and hand joints of the affected UL.

The follow-up data were slightly different to the present study. The study by Hesse et al. (2011) showed an improvement of 4 points from post-intervention to follow-up compared to 0.4 point change in the sub-acute group of the present study. However, it still implies that participants retained their improvements even after three months. Hesse et al. used an intensity of two mA as opposed to the one mA current used in the present study. Increasing the current of tDCS might not make a difference in the results. A variety in the selected current intensity from onemA to two 2mA is also very prominent in similar recent studies involving tDCS and rehabilitation (Bolognini et al., 2011, Lindenberg et al., 2010). However, there is not enough supporting evidence for the increase in current intensity on UL motor recovery in stroke.

The present study was the first study exploring the use of three-dimensional unilateral therapy in addition to anodal tDCS for people with chronic stroke with follow-up data. A small study combined bilateral RT in addition with tDCS involving people with chronic stroke (Ochi et al., 2013). The study involved 18 participants with chronic stroke in a randomised double-blinded cross-over study. The study involved the bilateral RT and 1mA cathodal or anodal tDCS. They found a small significant improvement in FMA after both types of stimulation however, the p-value of the significance level was not presented. As reported in the meta-analysis section of this thesis (Chapter three) the study by Ochi et al.(2013) scored a fair score for its methodology. The randomisation process, the length of the rehabilitation programme and also the blinding procedure of the participants were not explained in the study. Therefore, one has to interpret the results with caution.

In the present study non-significant differences were found between real and sham tDCS on UL function and dexterity. tDCS was placed on the arm and hand region of the motor cortex however, the Armeo®Spring robot training did not promote complex hand movements which could be the reason why significant improvements were not found. In addition, modelling studies have shown that electric current can accumulate at the edge of the gyri, therefore this might have decreased homogenous stimulation in this case on the upper limb motor cortex (Datta et al., 2009). Similar studies involving RT and tDCS also measured UL function and dexterity (Mathiowetz et al., 1985, Edwards et al., 2009, Hesse et al., 2011). Non-significant differences were also reported between the real and sham groups (Hesse et al., 2011). In the aforementioned studies, the robot also did not promote hand movements and which could be one of the reasons for non-significance.

Constraint Induced Movement Therapy, a rehabilitation technique that promotes hand use, was combined with bihemispheric tDCS on hand function (Bolognini et al., 2011). In June 2013, unlike RT, CIMT was recommended as a form of treatment for the arm and hand by the National Institute for Health and Care Excellence (NICE) guidelines for stroke rehabilitation (Drummond et al., 2013). Significant differences in hand function in the group receiving bihemispheric stimulation and CIMT compared to the sham stimulation was found which also remained stable at follow-up (Bolognini et al., 2011). This is a small study involving 14 participants with chronic stroke however, the results were different to the ones reported in Hesse et al. (2011). This could be due to the different clinical measure used, the severity of the hand function of the participants involved in the studies and the rehabilitation assistive technologies used in the studies were completely different to each other (RT and CIMT). The effect of tDCS and rehabilitation on UL ADLs and stroke impact was never addressed in studies involving larger samples with sub-acute stroke (Hesse et al., 2011). UL impairments have been positively associated with the quality of life of people with stroke. Therefore, it was essential to understand how the intervention has influenced factors such as emotion, memory, communication and participation of the participants (Nichols-Larsen et al., 2005).

Therefore, with regard to UL impairments and hand function inconsistent results were demonstrated when comparing real to sham tDCS stimulation groups in previous research which is probably due to the chosen rehabilitation programmes and type of tDCS. Inconsistent results regarding changes in cortical excitability after the intervention were also found in the present study which is discussed in the following section.

6.4.2.3 *Effect of robot therapy and transcranial direct current stimulation on cortical excitability*

In the literature, an increase in cortical excitability was presented from the combination of tDCS and rTMS with rehabilitation (Liepert et al., 2000, Edwards et al., 2009, Bolognini et al., 2011, Khedr et al., 2013). The RMT is the minimal intensity applied by TMS in order to evoke a MEP with an amplitude 50 (µV). In people with stroke, the RMT is usually higher than in healthy people (Platz et al., 2005b). Therefore a higher TMS intensity is generally needed to elicit a MEP in stroke. In the present study, the MEP was not elicited in three out of five participants at post-intervention. This could be due to several reasons. First, responses to TMS in severely affected participants are usually absent (Berardelli et al., 1987). As was observed in the present study, people with moderate to mild UL impairments have higher thresholds and small MEP amplitudes (Heald et al., 1993).

There are also other factors that affect the outcome of the TMS measurement such as participants' alertness and certain medications. The RMT depends to the neural membrane excitability and therefore pharmacological medications alter the sodium and calcium levels at the synapse and thus modify the RMT (Dimyan and Cohen, 2010). In addition, certain stages of the menstrual cycle and cortisol levels have shown to affect the MEP response (Smith et al., 1999, Sale et al., 2008, Sale et al., 2010). The measurement takes a long time to administer and therefore, the orientation and position of the coil held by the researcher can change over time (Sparing et al., 2008, Ahdab et al., 2010). Ideally, in the present study measurements from the unaffected hemisphere would also have been carried out in order to compare MEP responses with the affected hemisphere, however, due to time constraints this was impossible to be conducted.

After a stroke, the amplitude of MEP elicited from the affected hemisphere is smaller with increased latency when compared to stimulation of the unaffected hemisphere (Platz et al., 2005b). Recruitment curves of only two participations were measured in the present study. From the curve of P02, it was noticed that there was not much change in from the baseline to the post-intervention curves. As mentioned in the previous section, the variability could depend on the medication taken by the people with stroke, and the level of fatigue and alertness during the assessment (Dimyan and Cohen, 2010). The recruitment curve of P06 showed an increased in MEP amplitudes at 100% RMT at post-intervention and follow-up. This was expected and also reported in studies involving tDCS (Hummel et al., 2005, Khedr et al., 2013) and repetitive TMS (Peinemann et al., 2004, Castel-Lacanal et al., 2009). Large trials involving RT and tDCS did not include neurophysiological measures and this was probably due to the participants having severe UL impairments (Hesse et al., 2011). Corticospinal excitability was measured after tDCS and RT and an increase in MEP amplitude after the intervention was demonstrated (Edwards et al., 2009). However, this present study involved the data from only six participants with stroke. It is therefore difficult to make any conclusions about the effect of tDCS and rehabilitation on cortical excitability using TMS. On the other hand, there is a lack of research demonstrating the standardisation procedure of the assessment and this will be discussed in sub-section 6.6.2.

In summary, from the present study it was found that there is not enough evidence that adding on tDCS increases the benefit on UL impairments, activities and cortical excitability. These results are similar to the largest study to date, however, contradict studies involving bihemispheric stimulation. From the meta-analyses described in Chapter three, it was shown that only bihemispheric tDCS showed a positive but small effect on the UL improvements compared to sham stimulation in people with chronic stroke (Lindenberg et al., 2010, Bolognini et al., 2011).

6.4.3 Views and experiences of the participants about the intervention

Conducting qualitative in addition to quantitative research was important in order to obtain a deeper understanding of human experiences (Polit and Beck, 2010). This is the first study to explore the views and perspectives of non-invasive brain stimulation in addition to RT in stroke.

All the participants were interviewed and three important themes were obtained from the analysis. The feasibility issues have already been discussed in relation the first theme. The second theme focused on the “effects of treatment” including the sub-theme “motor effects”. From the structured questions, 86% of the participants felt that activities with their affected UL had improved which gave them confidence using it during two-handed tasks such as cutting their food and gardening. Lack of confidence is experienced by people with stroke. Re-integration in the community and carrying out exercise programmes has been shown to increase levels of confidence in people with stroke (Reed et al., 2010).

Some participants felt that their performance was better when the tDCS was switched on. However some disagreed and thought that the RT improved their activities. This in fact, coincides with the quantitative results. Nearly all participants (90%) expressed positive experiences such as fun and increasing their motivation from RT. This was also reported in a smaller focus group study involving five people with stroke exploring the use of assistive technologies for the UL in stroke (n=5) (Demain et al., 2013). However, in a larger questionnaire study involving 99 people with stroke also exploring the latter aim did not complete any questions about RT due to the lack of use in their rehabilitation programme. Health care professionals (n=292) also thought that robots were durable, fun to use and evidence- based however factors such as cost and unsuitability for home use are probably the prime reasons why they are not being used in clinical practice (Hughes et al., 2013). As a result, the National Clinical Guidelines for Stroke recommend that RT should only be used as an adjunct to conventional therapy when the main goal of the person with stroke is to minimise arm impairment or in the context of a clinical trial (Royal College of Physicians, 2012).

Most of the participants (81%) thought the stimulation was comfortable however, the choice of adding tDCS with stroke rehabilitation programmes requires some reflection and speculation.

6.5 Reflections on tDCS as an intervention with upper limb stroke rehabilitation

This was the first study to combine uni-lateral and three-dimensional RT with anodal tDCS for the impaired UL and stroke impact in stroke. However, the results of the present study and similar studies have shown that combining anodal tDCS with rehabilitation programmes such as RT does not lead to significant UL improvements. However, the study was under-powered and there was a trend favouring real anodal stimulation compared to sham stimulation for improving UL impairments. Possible factors affecting this result include (a) type of direct current stimulation (b) intensity of stimulation (c) frequency and duration of the intervention and (d) responders and non-responders (Figure 6.2)

6.5.1 Type of direct current stimulation

The choice of anodal tDCS for the present RCT was based on the existing research at the time of protocol developement which reported significant changes when anodal tDCS was added to a RT programme for the UL in stroke involving ten participants with chronic stroke (Hesse et al., 2007). From the current findings of the present study and a larger study carried out by Hesse et al., (2011), the benefits of using anodal tDCS with people with sub-acute stroke need to be speculated. Single sessions of anodal tDCS have improved reaction times in people with sub-acute and chronic stroke (Hummel et al., 2005, Stagg et al., 2012, Marquez et al., 2013). This has been linked with decrease in Gamma-Aminobutyric Acid (GABA) levels of the positively stimulated motor cortex and increased functional connectivity within the motor areas of the brain (Stagg et al., 2009). Insufficient detail is known about neurophysiological changes when combining multiple sessions of tDCS with rehabilitation programmes in people with stroke, especially in the acute.

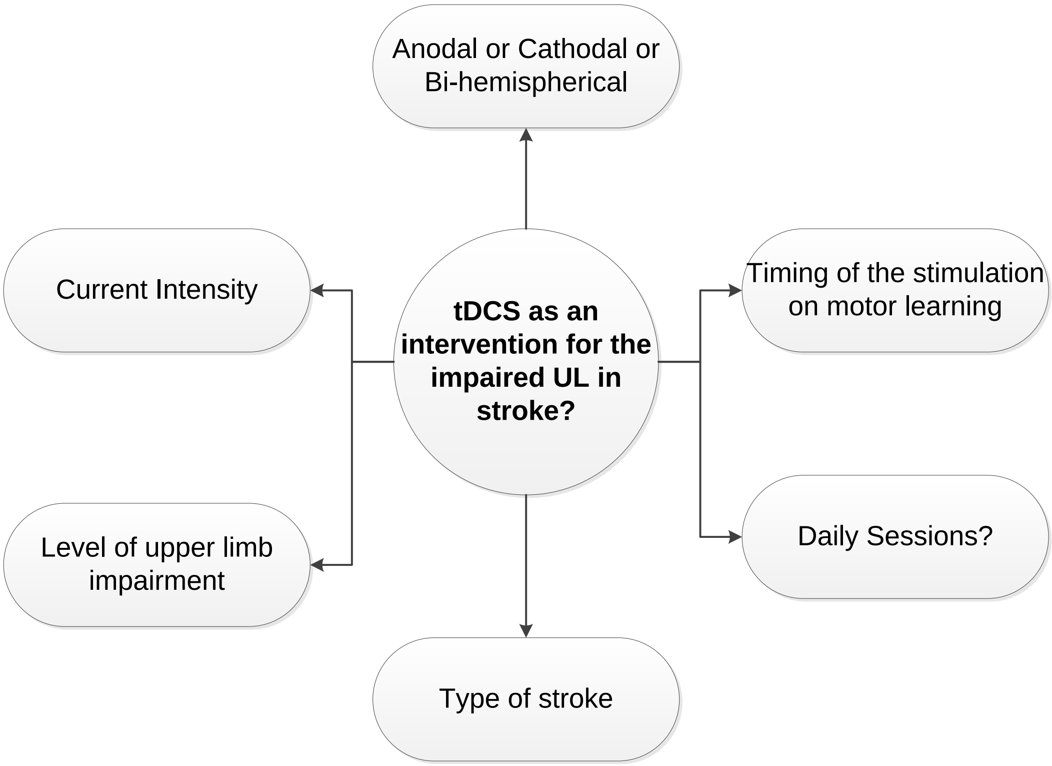

Figure 6.2 Factors to consider when applying tDCS in stroke rehabilitation

Mixed results have been demonstrated, when cathodal stimulation was used for the UL in people with chronic stroke (Stagg et al., 2012, Fregni et al., 2005). Imaging studies have shown that cathodal stimulation can increase activity in the ipsilesional hemisphere. However these changes were not translated to changes in reaction times of the UL. In spite of this, there is some evidence that cathodal stimulation can be more effective in mildly affected participants than severely affected participants (Bradnam et al., 2012). Inter-hemispheric imbalance has been found to be greater in people with stroke with a poorer recovery (Ward et al., 2003a, Ward et al., 2003b). Researchers have debated whether the increased activity in the contra-lesional motor and premotor cortex acts a form of adaption (Johansen-Berg et al., 2002, Lotze et al., 2006). Therefore, cathodal stimulation in people with severe UL might disrupt this adaptation and therefore worsen motor performance (Amadi et al., 2014).

From the meta-analyses described in Chapter three, it was shown that bihemispheric tDCS showed a positive but small effect on the UL improvements compared to sham stimulation however only in people with chronic stroke (Lindenberg et al., 2010, Bolognini et al., 2011). Greater activity has been found in bilateral M1 during bihemispheric stimulation as compared to anodal stimulation (Lindenberg et al., 2013). However, in the latter study older adults were studied and therefore, the adverse effects of applying bihemispheric stimulation to people with acute and sub-acute stroke is still unknown. Such an electrode montage might also disrupt the inter-hemispheric imbalance that occurs after a stroke (Nowak et al., 2009).

Future research should investigate the effects of bihemispheric tDCS in participants with sub-acute stroke. In addition, research focus has also been diverted to using high definition tDCS. Through this technique electric fields can be accurately targeted to the motor cortex rather than the conventional approach that was used in the present study (Dmochowski et al., 2011). This could be further researched for studies involving people with stroke and RT.

6.5.2 Current intensity of direct current stimulation

A varied methodology in the provision of tDCS has also been very prominent in all the studies involving rehabilitation programmes for the UL in stroke. The evaluated tDCS studies used different intensities of 1 or 1.5 or 2mA. Increasing stimulation intensity might lead to increased UL movements since the efficacy of stimulation can depend on intensity (Teo et al., 2011). Researchers may have had a good justification for the choice of tDCS intensity, but all failed to mention the rationale behind their choice. A recent study showed a non- significant difference in the learning curve and motor performance between 1mA and 1.5mA in healthy participants (Cuypers et al., 2013). In addition, no significant differences were found between groups receiving a gradual increase of intensity to 2mA per session to those receiving maximal dose of 2mA during all the sessions over five consecutive days (Gálvez et al., 2013). Future work should include a proper justification for the increased intensity and also provide a detailed report about any adverse events experienced by people with stroke.

6.5.3 Frequency and duration of the intervention

In all research studies involving multiple sessions of tDCS and rehabilitation programmes, the frequency and duration of the invention has also varied. Hesse et al. (2011) included a long treatment programme of 30 sessions whilst Lindenberg et al. (2010) included only five sessions. Most of the studies included daily intervention sessions. In healthy volunteers, the effects of tDCS on cortical excitability and performance are short-lasting and variable (Nitsche and Paulus, 2000, López-Alonso et al., 2014, Wiethoff et al., 2014). However, it is usually assumed that repeated daily applications in stroke may lead to a build-up of effects that are larger and more persistent. The main evidence in favour of this comes from studies of repetitive TMS to treat depression: a single session, or even two weeks daily treatment with repetitive TMS has little effect on symptoms over and above placebo, whereas longer treatments can improve symptoms for several months (Lam et al., 2008). Thus most recent clinical trials of tDCS have employed several days or weeks of repeated treatment in an attempt to maximise outcome. Interestingly it is still unclear whether repeated daily session of tDCS have cumulative effects in the healthy population (Alonzo et al., 2012, Monte-Silva et al., 2013). Therefore, one cannot make any accurate conclusions about the administration about daily sessions until larger studies will be carried out. Thus, this needs to be addressed when developing a standardised protocol of tDCS in stroke rehabilitation.

It is still debatable whether one should apply tDCS during, before or after skill learning. Non-invasive brain stimulation facilitates activities in cortical regions that are involved in motor learning (Reis et al., 2008). Evidence shows that if anodal tDCS is applied during motor learning it can result in faster learning than if applied prior to motor learning (Stagg et al., 2011). tDCS might improve motor skill learning through augmentation of synaptic plasticity including GABA levels within the primary motor cortex (Fritsch et al., 2010). A reduction in neurotransmitter GABA has been associated with learning and performance improvements (Floyer-Lea et al., 2006). From the systematic review presented in Chapter three, it was showed that the majority of studies applied tDCS during the rehabilitation programmes. This reduces the time of intervention and might also induce an accumulative effect for motor learning. However, the present study and studies by Hesse et al., (2011) involving participants with sub-acute stroke have failed to show a significant effect with the combination of anodal tDCS and RT and this could be due to potential inhibition of skilllearning during simultaneous technologies. Intensive and complex interventions such as RT might be over-riding the motor learning effects that are occurring during tDCS.

6.5.4 Responders and non-responders to the intervention

Ultimately, the key issue is which patients with stroke are most likely to benefit from tDCS and rehabilitation regimes. There also seems to be a lack of evidence about which types of tDCS might be more beneficial for people in the acute or the chronic phase of stroke. In addition, it is unknown whether adding tDCS is more important for people with mild or severe UL impairments. For instance there is limited evidence that RT is more beneficial for people with moderate UL impairments compared to severely affected people with stroke (Ferraro et al., 2003).

From the present study, there was a clear indication that participants with mild and moderate UL impairments showed a better UL and hand recovery compared to participants with severe impairments (refer to Figure 4.28 on page 143) and this in agreement with previous research (Coupar et al., 2012). However, this is in contradiction to previous robot research which states that RT is more beneficial for people with moderate to severe UL impairments (Fasoli et al., 2003, Lo et al., 2010, Liao et al., 2012). This could be linked with factors such as sub-cortical or cortical stroke.

Recovery after a cortical stroke is often more difficult to achieve compared to a sub-cortical stroke (Hesse et al., 2007). In the present study, sub-cortical stroke was found to be a significant predictor for enhanced UL recovery (refer to Table 4.8 on page 142). Different patterns within the brain are enhanced for UL recovery in cortical and sub-cortical strokes (Buma et al., 2010). Research has shown that motor practice following stroke results in changes in the motor cortical areas and sub-cortical areas (Carey et al., 2002, Luft et al., 2004, Bosnell et al., 2011). As opposed to a sub-cortical stroke, the GABA-ergic intra-cortical inhibition is increased after a cortical stroke which could be associated with enhanced glutamatergic activity (Buchkremer-Ratzmann and Witte, 1997). It is still inconclusive whether adding on tDCS leads to better results in people with sub-cortical strokes. Hesse et al. (2011) showed that people who had a pure sub-cortical stroke and received cathodal stimulation had a significant effect on the FMA post-intervention score. In the present study, due to the small sample, no significant differences were found between the anodal and sham groups. Future research should further speculate the effect of all types of tDCS with cortical and sub-cortical strokes.

Stratification of participants according to their stage or location of the stroke or UL severity might be the first steps in identifying good or poor responders to tDCS. After acquiring more information about the aforementioned predictors, the appropriate selection of type of tDCS and outcome measures can be carried out when developing a research protocol.

6.6 Outcome measures chosen for pilot RCT

The clinical findings obtained from the RCT were discussed. However, in order for findings to be accurately analysed discussion and speculation about psychometric properties such as responsiveness and reliability of some of the outcome measures chosen for the RCT is required.

6.6.1 Responsiveness of UL impairment outcome measures

Responsiveness is the ability for an outcome measure to detect change over time (Gladstone et al., 2002). FMA was chosen as the primary outcome measure due to its excellent validity and reliability in stroke and it also enabled comparison of the data of the present study with similar studies using the same measure (Malouin et al., 1994, Platz et al., 2005a). However, the responsiveness of FMA outcome measure needs to be questioned. A floor effect can be demonstrated and it may lack responsiveness in people with moderate and severe UL impairments (Gladstone et al., 2002). One of the assessments as part of FMA, was UL co-ordination. In order to test it, the affected UL, had to be at a starting position of shoulder abduction at 90º. This was impossible for the majority of the participants due to lack of strength and pain. Thus, including the assessments of the Armeo® Spring robot provided more accurate information than human administered clinical scales. However, clinical scales are still assumed as the ‘gold standard’ for measuring impairments (Bosecker et al., 2010).

Responsiveness of the ARAT has been shown to be higher than FMA in people with chronic stroke (van der Lee et al., 2001). However, as presented in our study floor and ceiling effects were also demonstrated in the ARAT when measuring UL function and dexterity (Platz et al., 2005a). A potential limitation of the ARAT was that some tasks were too difficult for people with sub-acute stroke. Also, the shelf was too high for participants who have shoulder pain during 180º shoulder flexion. This resulted in increased compensatory trunk movements during the measurement. Adding another measure such as the Wolf Motor Function test which has been developed for people with UL problems after mild or moderate stroke, could avoid this problem (Wolf et al., 2001). One must note that a floor effect might also be demonstrated with this measure in people with severe UL problems (Rabadi and Rabadi, 2006).

6.6.2 Reliability of cortical excitability measurement using TMS

Due to increased variability discussed in Section 6.4.2.2, the psychometric properties of the measure of MEPs using TMS in stroke has been questioned (Wiethoff et al., 2014). Therefore, a small study involving healthy age-matched adults (n=21) was carried out to explore the intra-rater and test-retest reliability of the RMT and MEP amplitude of the distal muscle Extensor Digitorum (ED) and the proximal muscle Anterior Deltoid (AD) on the same day (test 1 and 2) and on separate days (tests 1 and 3).

The RMT at ED and AD muscles had excellent intra-rater and test-re-test reliability in all the participants (refer to Table 5.2 on page 211 and Table 5.3 on page 214). In a previous study, excellent to moderate reliability (ICC=0.60-0.92) was also reported however when measuring MEP thresholds in young adults (Livingston and Ingersoll, 2008). The present study was the first to measure the minimal detectable change of the RMT and MEP amplitude. If percentage changes in RMT are found after clinical trials involving tDCS, the researchers can potentially refer to the minimal detectable change. However, one must note that the study was carried out with a small sample of healthy adults and therefore, the results are not applicable to people with stroke.

Reliability analysis showed that the MEP amplitudes for the ED between tests 1 and 2 had poor to moderate level of agreement with wider confidence intervals for intensities ranging from 100-150% of RMT. Poor reliability for MEP amplitude of hand muscles was also found in young adults (ICC = 0.01 to 0.34) (Kamen, 2004, Livingston and Ingersoll, 2008). Only one study explored the reliability of MEP measurement at the hand extensor muscles in chronic stroke and large fluctuations in MEP amplitude between sessions were demonstrated (Andrew et al., 2005).

The present study was the first to explore the reliability of MEP amplitude of the AD muscle. Reliability analysis showed that the MEP amplitudes for the AD had moderate to excellent level of agreement for MEP amplitudes at TMS intensities 100-120% (ICC=0.527-0.903), however with wide confidence intervals between tests 1 and 2 on the same day. Although, a poor level of agreement was found at 100% of RMT, a moderate to substantial agreement was found at intensities 110% and 120% of RMT between tests1 and 3 for the AD muscle. On the other hand, high intra-class correlation coefficients were found for the biceps brachii MEP amplitude (ICC=0.95-0.99) in young adults. One must note that the latter study used a circular coil which is less focal than the figure of eight coil (Rösler et al., 1989).

In the present study, older adults had an excellent and stronger agreement (ICC=0.956) than the younger adults group for RMT of ED between tests 1 and 2, however this opposes other studies. Comparing between tests 1 and 3 the younger and older adults showed moderate the level of agreement (ICC=0.587 and 0.60). There evidence shows that older adults had higher RMTs compared to younger adults, however stimulus-response characteristics are not altered with age (Pitcher et al., 2003, Oliviero et al., 2006, Smith et al., 2011). Therefore, not including older participants in clinical trials due to age is not the appropriate choice. However, there is conflicting evidence that factors such as gender (Wassermann, 2002, Inghilleri et al., 2004) and genotype (Cheeran et al., 2008, Voti et al., 2011) can influence RMT and MEP amplitude measurements. Moreover, time of day and caffeine use has also been shown to affect the MEP response (Cerqueira et al., 2006, Sale et al., 2007).

Therefore, the reliability study showed that RMT had excellent reliability at both muscles. However, MEP amplitude measurment had moderate to poor reliability. Clinical studies have reported that anodal tDCS can lead to increased cortical excitability by measuring MEP amplitude. However, such assumptions cannot be made knowing that this measurement provides variable results on separate days. Using functional Magnetic Resonance Imaging (fMRI) or Magnetic Resonance Spectroscopy or diffusion tensor imaging could be an alternate option for exploring cortical changes induced by tDCS within the brain. However, this increases the total cost of the research and fMRI lacks time resolution (Hallett, 2000, Stagg and Johansen-Berg, 2013).

6.7 Limitations of the research

The results of the present study have to be analysed with caution due to several limitations related to the systematic review, RCT, reliability study and the statistical analyses.

6.7.1 Systematic review and meta-analyses

Although a small, but non-significant trend of benefit was demonstrated, one must mention that this review had its limitations. This review only contained a small number of papers and therefore most meta-analyses could only be conducted with two studies. In addition, only post-intervention data was included in the meta-analysis due to the program chosen. Ideally the baseline data would also have been included in order to compare with the post-intervention data. However the program used, Review Manager (a program that is used for preparing and maintains Cochrane Reviews), does not have this option (CochraneCollaboration, 2011). Additionally, due to the software used, data involving medians could not be involved in the analyses. Software such as Comprehensive Meta-Analysis by Biostat® allows input of baseline data which should be considered for future reviews. However, this program is not free and requires additional training which were the main reasons why it was not used for the present study.

6.7.2 Pilot RCT

The limitations involved in the pilot RCT are discussed in the following sub-sections. This is discussed in relation to the ethical approval and recruitment, sample and delivery of intervention.

6.7.2.1 Ethical approval and recruitment

The main recruitment source of people with sub-acute stroke was through National Health Service (NHS) Trusts. This process involved seeking approval from the NHS Ethics Committee and approval from Research and Development department at each of the seven NHS sites. Overall, this process took around a year to process and finalise which delayed the initiation of recruitment.

The present study was not portfolio adopted by the Comprehensive Clinical Research Network. Therefore, in some NHS sites, the research nurses employed by the National Institute for Health Research could not help out to identify participants for the trial. The rationale for this was that the NIHR did not recognise the funders for the study as a priority. Therefore, this did not help the recruitment process and the main researcher (LTT) had to go to each NHS site on a weekly basis and enquire if there were any eligible participants. This lengthy process reduced the recruitment period of participants with sub-acute stroke for the research trial. Future research should plan and take this time in consideration when carrying out projects involving people registered with the NHS.

The eligibility criteria were quite tight and therefore, finding participants that met the criteria was very difficult. Once the trial was commenced, it was noted that factors such as problems in neglect and vision were not included in the criteria. These factors might had caused flaws in the data collection and the participant experiencing difficulties seeing targets during the assessment procedure of the robot. The latter factors are very important factors to be considered as exclusion criteria for future trials involving RT.

6.7.2.2 The sample for RCT

The sample included in this study was heterogeneous due to the different phases (sub-acute and chronic) of the stroke, types and locations of their stroke, baseline UL impairments and handedness. No significant differences were found for UL impairments and age between the real and sham groups. However, different handedness, stroke type and location could have been confounding factors. Moreover the participants with chronic stroke had a higher UL tone at baseline than the sub-acute stroke. Also, participants continued with their concomitant treatment with an average of twice a week during the trial and the three-month follow-up period. One participant was taking anti-depressants which could have enhanced the tDCS effect on cortical excitability. Although excluded from the TMS assessment future studies involving tDCS should exclude participants taking anti- depressants and therefore minimise any further confounding factors.

6.7.2.3 Assessment procedure and outcome measures

Overall, the assessment procedure lasted longer than expected. Due to level of fatigue and also the participants having other commitments, the assessments were carried out on average three days before the baseline and three days after the last robot session. This delay might have caused a decline of the improvements achieved from intervention. Additionally, assessments were only carried out once at baseline, post-intervention and follow-up. Therefore, the level of variability cannot be detected across days.

The clinical assessments were carried out by three different assessors. The assessors were trained by the same person (LTT) and had experience carrying out the assessments with patients with neurological conditions. However, an increase measurement error between the assessments could have occurred. The measurement error (± 2 standard error of the mean) was reported at ± 7.2 for the FMA UL motor score and this was analysed for multiple raters (Sanford et al., 1993). Therefore, this level of measurement error needs be acknowledged in the interpretation of the FMA results. However, all the assessments were recorded and rated again by an additional clinician. Any disagreements were discussed by the two raters and this potentially increased the level of consistency.

As mentioned in the feasibility section, some participants felt that the amount of questions asked during the assessment process was burdensome. The MAL, SIS and HAD outcome measures were administered at the beginning of the session. Therefore, this could have influenced their level of fatigue and tone whilst carrying out FMA and ARAT and RMT. If the SIS, MAL and HAD were carried out at the end of the assessment process, fatigue could have been avoided and possibly some participants would have achieved a higher score on the UL clinical measures and also better MEP responses.

The angle of catch was measured by a goniometer and there has been evidence that this type of measurement is not reliable (Armstrong et al., 1998).

It has been recommended that measurement of spasticity should include surface EMG in order to measure the neurophysiological properties of spasticity and also a force transducer to measure the biomechanical properties of spasticity (Malhotra et al., 2008). These technologies were not used in the present study since they would have increased the length of the assessment procedure.

Some of the participants felt that they were not given a valid reason for the questions asked about the stroke and depression. This probably caused psychological stress and should be avoided especially at the start of the assessment session. Emotional problems such as depression, anxiety, apathy and anger are very common after a stroke (Kneebone and Lincoln, 2012). Therefore, in order not to exacerbate these emotions, it is essential that during future research, before an outcome measure will be used, appropriate information should be provided to the participant.

It would have been ideal if before each TMS assessment of the participant with stroke, a MRI scan of that person was uploaded onto the neuronavigation system. However, most of the NHS sites do not capture MRI Scans when an individual has a stroke. Thus, the standard MRI provided with the equipment was used for all the TMS assessments which might have not been a true representation of the participants' motor cortex.

Additionally, as one can note from the results section that MEPs were sometimes not elicited during the assessment and therefore, this can be very time-consuming and tiring for the participant with stroke. Some of the participants were falling asleep at some point during the assessment since it does not require any participation. It was important that all assessments (clinical and neurophysiological) were carried out on the same day and therefore, this prolonged the assessment time of the participants. Removal of the measurement of the active motor threshold limited the data to solely the neurophysiological properties of the muscle at rest rather than during activity. Moreover, the EMG equipment available at the University was not ideal to be combined with the Magstim TMS equipment and measure MEPs. The signal was not amplified during measurement and therefore it was time-consuming to view small MEP responses of 50 (μV). In the future, the equipment ‘Signal’ (Cambridge Electrode Design) should be used in addition with the EMG equipment since this is more compatible, feasible and provides amplification during the measurement of MEP responses. In order not to increase the time of the assessment and increase anxiety for the participants, the skin hair was not removed for the EMG measurement. Therefore, adhesion of the electrodes was sometimes affected due to sweat or movement resulting in increased skin impedance.

6.7.2.4 Delivery of the intervention

During the months of June and July 2013, two researchers carried out the intervention process. This increased the efficiency of data collection, however this might have caused some inconsistencies in the intervention administration. The verbal prompting and assistance provided by the researcher might have been different during the sessions.

With regard to the tDCS intervention, the equipment used only applied direct current for ten seconds during sham stimulation. Nitsche et al. (2008) recommended that this should be on for 30 seconds and therefore, participants might have been aware of the short stimulation time. In addition, the adhesive bandages used to attach the electrodes to the motor cortex, kept sliding forwards especially in females. This prolonged the time of placement of the electrodes before the intervention was commenced.

With regard to the RT intervention there were some problems with robotic arm. Each time a heavy weight UL was placed in the robotic arm, the spring was not strong enough to maintain the weight of that UL and therefore the anti-gravity action was lost. Therefore, the researcher had to provide extra support whilst the participant was playing the games. Also, participants with severe UL impairments tended to have increased trunk movements when moving the robot arm. Increased compensatory trunk movements could have resulted in the UL movement gain.

Ideally, the researcher carrying out the intervention would also have been blinded. Knowing the type of stimulation being applied to the participants might have caused some bias. Therefore, it would have been more scientifically sound if the study was triple-blinded. Also, the fact that participants were allocated to either the ‘sham’ or ‘real’ group, participants were constantly questioning whether they were receiving the stimulation or not. This could have interrupted their concentration during RT.

6.7.2.5 Qualitative component

The participants were interviewed immediately after the post-intervention assessments. Therefore, participants were probably slightly tired for the interview process. In addition, some participants might have not felt comfortable expressing negative experiences of the research due to the relationship built with the researcher (LTT) during the 18 sessions. This was the first study exploring the views and experiences about NIBS and therefore the questions were developed by the researchers of the project and not obtained from any previous studies or research. In addition, the interview guide was followed a structured process and therefore this could have narrowed down the views and experiences of the participants. Finally, LTT mainly carried out the data analysis. Although controlled by an external researcher of this project (Dr Maggie Donovan-Hall), researcher bias might still have influenced the results obtained for this study.

6.7.3 Reliability study

After the RCT was conducted, it was decided that a reliability study of the MEP measurmenet was needed. It would have been ideal if the reliability study was carried out prior to the pilot RCT. This would have resulted in more knowledge about the measurement technique and the psychometric properties of the measure for the researcher. In addition, the validity and the inter-rater reliability psychometric properties of RMT and MEP amplitude measurement were not examined in this study and therefore, could not be explored

The study did not involve participants with stroke and therefore intra-rater and test-retest reliability cannot be generalised to the stroke population. Additionally, the healthy participants were not selected randomly from the general population and therefore, the data cannot be generalised to all healthy young and old adults.

As discussed in the previous section, the signal of the EMG was not amplified during data collection. This might have caused flaws in reading the data when trying to obtain the 50 (µV) MEP responses. Less data was obtained for the AD muscle. The representation of this muscle in the motor cortex is very small compared to the middle deltoid muscle. If an electrode was placed on this muscle, more data would have been obtained for this muscle.

The tilt of the coil during data collection could have been subjected to human error due to prolonged holding time of the heavy coil by the researcher (LTT). Therefore, this could have affected the size of MEPs obtained during data collection.

6.7.4 Statistical analysis

For both the RCT and reliability study, a small sample size was included. Therefore, the results must be treated with caution. In addition, several statistical tests were applied to the data and therefore type 1 error could have occurred.

For the reliability study, a small dataset was inputted for analysis of the anterior deltoid and the difference between the left and right groups. Therefore, the data had high confidence intervals and reliability analysis of the anterior deltoid and the left and right groups must be interpreted with caution.

6.8 Conclusion

This chapter presented a discussion about the findings obtained from the three studies conducted for a Doctor of Philosophy degree. The feasibility component of the pilot RCT was examined and analysed: such as the recruitment process (including sub-acute and chronic participants) and sensations from the tDCS such as itching and burning and fatigue and pain from RT. The results from the systematic review and reliability were also discussed and applied to the clinical findings from the pilot RCT. In general, a clinically significant improvement was noted in UL impairments, activities and stroke impact at post-intervention and follow-up in the sub-acute group. However, a significant improvement was only found for UL impairments at post-intervention and stroke impact at follow-up for the chronic group. These findings were compared to similar studies involving tDCS and rehabilitation programmes. From the qualitative research, the views and experiences were linked in with feasibility component, the effect of treatment and areas for development. Participants enjoyed the RT sessions, however they also provided feedback how future research can be improved. The findings therefore have implications for clinical practice and future work and these are discussed in the following chapter.

Chapter 7

Implications for Clinical Practice and Future Work

7.1 Introduction

This chapter focuses on the implications of the results of the research for clinical practice. This is followed by a detailed plan and discussion about future work.

7.2 Implications for clinical practice

The research that has been presented in this thesis focussed on one main problem that is experienced by people with stroke. At six months post-stroke, only 5-20% percent achieve full recovery (Kwakkel et al., 2003, Kwakkel and Kollen, 2013). Current rehabilitation techniques used in clinical practice need to improve; poor Upper Limb (UL) outcomes post-stroke have implications not just for the individual, their carers, but also society (Demain et al., 2013).

Within this study an intensive, repetitive and task-specific RT programme targeting the UL was provided. An important clinical finding was that improvements in UL impairments were found for people with sub-acute stroke. However, the participants stated that they felt abandoned by the National Health Service (NHS); no rehabilitation was being provided for their arms. Chronic stroke participants stated that they believed it would have been beneficial if the RT rehabilitation programme had been provided during their hospital rehabilitation and in the early stages of their stroke. RT is rarely provided as a standard treatment in NHS settings. Through this research, the robot was one of the first robots to be integrated in a NHS community hospital in United Kingdom. Such an achievement showcases the potential for integration of technologies in the health service, providing new treatments for patients with stroke. Health care professionals within the hospital were trained in the provision of RT. The Armeo®Spring robot remains at the hospital and currently being used by the clinicians at Christchurch Day Hospital.

Another important clinical finding is that participants with chronic stroke also showed an improvement in UL impairments. People with stroke receive very limited rehabilitation due to restricted resources. This is also likely to be influenced by the concept of ‘plateau’ within motor recovery. However this research, in common with other findings, has demonstrated that people with stroke can improve UL movement even many years post-stroke. This potential for improvement is not being fully exploited.

As well as demonstrating improvements in UL impairments for the participants, this study promoted stroke community re-integration. The participants found RT fun and motivating. Adherence to the programme was very high; only one participant did not complete the study due to side effects from the tDCS. The present study did not include control groups with participants only receiving conventional therapy and therefore conclusions cannot be carried out about the benefit of RT over and above conventional care. However, there is evidence which shows that RT leads to better improvement of UL impairments than conventional therapy (Lo et al., 2010, Norouzi-Gheidari et al., 2012).

The application of non-invasive brain stimulation in clinical practice is in its infancy. The current clinical trial and systematic review showed that combining transcranial Direct Current Stimulation (tDCS) with rehabilitation techniques such as RT had a small effect on UL impairments. This could have been due to several factors such as current intensity and whether adding on stimulation affects the motor learning process. Previous small studies have shown that adding tDCS resulted in better UL movements. However, combining tDCS with intensive rehabilitation techniques such as RT did not lead to an additional improvement. However, further research involving Randomised Controlled Trials (RCTs) needs to be carried out in order to make accurate conclusions.

To establish the clinical effectiveness of combining technologies such as tDCS with standard rehabilitation in clinical practice, requires further research with larger sample sizes. A large RCT is currently being carried out in the UK called ‘Robot Assisted Training for the Upper Limb after Stroke’ by Dr Helen Bosomworth from Newcastle University. The researchers aim to recruit 720 participants at all stages of stroke. The study includes three groups: (a) RT, (b) intensive UL therapy and (c) usual care. The study should be finalised by 2017 and the results will provide more evidence about RT for the UL in stroke.

7.3 Future work and research

This section will focus on the planned future work and research based on the findings found from the research carried out for this Doctor of Philosophy degree. First of all, future work will involve publication of the findings from the three studies in peer-reviewed journals. The second section explains the systematic review with meta-analyses that will be primarily carried out in future research. The final section describes the RCT that will be carried out after the review.

7.3.1 Journal Publications

A final draft of the systematic review with meta-analyses is currently being reviewed by the authors of this paper and it will be submitted to the journal, <u>Brain Stimulation</u>*.* The quantitative component of the pilot RCT paper will be submitted to the journal, <u>Neurorehabilitation and Neural Repair</u>*.* The qualitative component of the pilot RCT paper will be submitted to the journal, <u>Physical Therapy</u>*.* The reliability study paper will be sent to <u>Clinical Neurophysiology</u>*.*

7.3.2 Systematic review and meta-Analyses

For future work, an updated systematic review and meta-analyses will be carried out primarily. This will give a picture of the current evidence and effect sizes of the different types of tDCS integrated with rehabilitation on UL impairments in stroke.

A detailed systematic review was conducted on papers published up until July 2013 which explored the combination of tDCS and rehabilitation programmes on UL motor impairments in stroke. This was presented and discussed in Chapter three. The selected articles were reviewed by two researchers involved in this project and qualitatively scored using the Modified Downs and Black form (Eng et al., 2007). This process ran smoothly and therefore, an updated review will be carried out involving a search of recent articles involving tDCS and rehabilitation programmes for the UL that were not included in the review in Chapter three.

These baseline data of the outcome measures is important for accurate meta-analyses. However these data are rarely published and therefore, will need to be obtained from the authors of the papers. In addition, for the previous meta-analyses, the program Review Manager 5.1, was selected for the analyses. However, this program is very basic and does not allow the input of baseline data of the outcome measures. Therefore, the software program Comprehensive Meta-Analysis will be used (ComprehensiveMeta-Analysis, 2006) and this will allow the researcher to input the baseline data. However, training will be needed to gain expertise on the use of the program.

7.3.3 Future RCT

A pilot RCT was carried out for this thesis and the main aim was to examine its feasibility and also test the effect of the combination of tDCS with RT for the impaired UL in stroke. The study was feasible with some adaptations. It identified ways in which the design could be improved to make it more feasible in future studies. These changes are based on the feedback provided by the participants and also analyses carried out by the research team discussed in section 6.2 of chapter six.

As suggested by the participants, the participation information sheet needs to have more detail about the evidence for the interventions in stroke. Stratification will still be carried out as the previous RCT but for the next trial the participants will be stratified according to level of UL impairment. This will provide more information about which type of participants will more likely to benefit from the intervention.

With regard to the intervention programme, overall the participants thought that the programme was intensive enough and therefore, the duration and length of the RT will not be changed. As was reported in previous qualitative robot research, several participants with chronic stroke did suggest home based rehabilitation (Demain et al., 2013, Meadmore et al., 2014). In the later stage of a stroke, people with stroke start feeling more ‘active’ which has been reported in several qualitative studies (Medin et al., 2006, Proot et al., 2007). Having home-based therapy may enhance these feelings and also independence. The Armeo®Spring robot is too large and heavy to be transported between the participants’ homes. If a new smaller three-dimensional robot such as the

Armeo®Boom (Hocoma AG), however with a more advanced hand module will be developed, purchase will be considered (Figure 7.1).

Figure 7.1 Armeo®Boom Robot which can be used at the participants' home (Image courtesy of Hocoma AG)

Participants could then have a choice whether to carry out the rehabilitation programme at their home or at a community hospital. New tDCS equipment is definitely needed for the future RCT. More advanced equipment displaying the level of impedance and the level of current inputted in the motor cortex should be purchased. This will improve the efficiency and reduce the likelihood of adverse events with the tDCS. In addition, as suggested by the participants, the adhesive bandages should not be used in future research and a head gear system should also be listed in the equipment needed for this research. The type of tDCS and current intensity will be based on the results of the updated systematic review and meta-analyses.

An appropriate choice of outcome measures will also be needed for the future trial. To ensure comparability with other studies, FMA will be used as a primary outcome measure, however, instead of measurement of MEP responses using TMS, functional Magnetic Resonance Imaging (fMRI) will be used as the second primary outcome measure. fMRI is sensitive to local blood oxygenation and also has high spatial resolution. However, one needs to keep in mind that that this technique has low temporal resolution. Adding on this outcome measure, will require support and continual supervision from experts within the field and as part of the research team. As secondary outcome measures, the previously described the Action Research Arm Test outcome measure will be replaced by the Wolf Motor Function test and a shorted version of the Stroke Impact Scale (SIS) will be used called SIS-16. This has been shown to be valid and reliable (Duncan et al., 2002). The Motor Activity Log-28 will be used because it gives an indication of the quality of the UL movements during activities of daily living. The Modfied tardieu scale and Hospital anxiety and depression scale will be removed. The progression of improvement will also be measured by the robot assessments at the beginning of every session, however the assessments need to be more user-friendly and specific.

Therefore, keeping these factors in mind, the research question will be: What is the effect of real tDCS versus sham tDCS in addition with RT for the impaired UL in stroke? Based on the Standard Deviation found from the FMA baseline score of the sub-acute and chronic group, four power calculations for a two group study were carried out (Table 7.1). These were based on a t-test comparing two independent samples.

Table 7.1 Estimated sample sizes of the sub-acute and chronic groups in order to obtain significance in the future trial

	Sample Size Sub-acute group	**Sample Size Chronic Group**
Power= 80% P value= 0.05	53	47
Power=90% P Value= 0.01	101	89

For a two-group study involving people with sub-acute stroke, at a power of 80% and p value of 0.05, each group must have 53 participants in order to obtain a significant difference. If the power is increased to 90% and p value set at 0.01, each group must have 101 participants. For the chronic group, at a power of 80% and p value of 0.05, each chronic group must have 47 participants whilst at a power of 90% and p value will be set at 0.01, 89 participants in each group will be needed.

7.4 Conclusion

This chapter presented the implications for clinical practice suggesting that RT needs to be integrated in acute and sub-acute stroke rehabilitation settings. In addition, further research is needed involving tDCS in order to be integrated within clinical practice. Future work will involve an update systematic review exploring the effect of tDCS with stroke rehabilitation for the UL in stroke. In addition, a larger double-blinded RCT will be proposed exploring the effect of real tDCS and sham tDCS on the UL impairments in stroke involving chronic and sub-acute participants. Few outcomes measures of UL impairments, activities and participation will be administered at baseline, post-intervention and follow-up. The next chapter presents the general conclusions of this thesis.

Chapter 8

General Conclusions

Conducting research is important to further the current knowledge on neurological rehabilitation of upper limb problems that are commonly experienced by people with stroke. The novelty of the research explored the combination of anodal transcranial direct current stimulation with uni-lateral and three dimensional robot therapy for the impaired upper limb and stroke in participants with sub-acute and chronic stroke by quantitative and qualitative methods. This research contributed to the current knowledge about adding transcranial direct current stimulation to rehabilitation programmes in stroke.

1) A systematic review with meta-analyses was carried out to explore the effect of tDCS with rehabilitation programmes for the impaired UL in stroke. Seven papers were included in the review and a small effect size was found between real tDCS in combination with rehabilitation programmes for the impaired UL in stroke.

2) Using a mixed-methods approach, a pilot double blinded RCT with a feasibility component involving 22 participants with sub-acute and chronic stroke was carried out. The feasibility and effect of anodal and sham tDCS in combination with three-dimensional uni-lateral robot therapy for the impaired UL in stroke was explored.

3) The feasibility analysis (including the recruitment process, intervention programme, and project resources) showed that the study was feasible however, checking for adverse reactions from tDCS needs to be integrated in to future work.

4) At post-intervention, participants with sub-acute stroke showed a significant clinical improvement of 15.5% in UL impairments and changes were maintained at three-month follow-up. Participants with chronic stroke also showed a clinically significant improvement of 8.8% at post-intervention, but these changes in UL impairments decreased by 4% at follow-up.

5) No significant differences were found between the real and sham tDCS groups however, sub-cortical stroke was found to be a predictor of better recovery of upper limb impairments.

6) The participants in the sub-acute group showed a significant improvement in upper limb function and dexterity and activities at post-intervention and follow-up. However, the chronic group did not show any significant differences. Additionally, the sub-acute group showed a significant decrease in stroke impact at post-intervention and follow-up but the chronic group only showed a significant decrease at the three-month follow-up.

7) Both people with sub-acute and chronic stroke reported that the intensive, repetitive and task-specific intervention programme was beneficial for both their upper limb and quality of life. The participants also gave suggestions for future research.

8) This research also involved a novel study exploring the intra-rater and test-retest reliability of the measurement of motor evoked potentials from the anterior deltoid muscle in healthy adults. It was found that measurement of the resting motor threshold of the anterior deltoid and even the extensor digitorum muscles had excellent reliability.

9) Measurement of the motor evoked potential amplitude of both muscles had moderate to poor reliability at 100-150% of resting motor threshold. The lack of reliability of the outcome measure provided information about appropriate selection of outcome measures for future research.

It was concluded that enough information was obtained from the pilot RCT and the changes and improvements will be applied to planned future research. Further meta-analyses and a larger randomised controlled trial involving transcranial direct current stimulation and robot therapy are required for future research. These will enable researchers and health care professionals to make accurate decisions when integrating transcranial direct current stimulation and robot therapy in stroke rehabilitation settings.

Appendix A

Systematic Review Sheets

A.1 Systematic review agreed scoring sheets

This section presents the scoring sheets of the included studies in the review.

Paper Code		**Kim et al., 2010**				
		Participant Numbers (N) =10		**>1**		
		Follow-Up? Yes 60 mins post		**Ye s**		
Downs and Black Questionnaire			**Comments**		**X**	**X Score**
Reporting	1	Is the hypothesis/aim/objective of the study clearly described?			Yes	1
	2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?			Yes	1
	3	Are the characteristics of the patients included in the study clearly described?	I		Yes	1
	4	Are the interventions of interest clearly described? Interventions have to be a comparison between equipment, protocol, rehab methods etc a one off measurement does not count			Yes	1
	5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?			Partially	1
	6	Are the main findings of the study clearly described?			No	0
	7	Does the study provide estimates of the random variability in the data for the main outcomes?			Yes	1

	8	Have all important adverse events that may be a consequence of the intervention been reported? For the paper to score yes the phrase "Adverse Events" has to be mentioned in the results/discussion/conclusion			Yes	1
	9	Have the characteristics of patients lost to follow-up been described? If there is no follow-up ie the study is just a single event study then the answer should be NO	.		Yes	1
	10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?			Yes	1
External validity	11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited? A single participant is not representative of the patient population as a whole			Yes	1
	12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?			Yes	1
	13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? This should be answered YES if you feel that the participants' treatment or care pathway, if stated, is similar to the larger population. If a novel or specialist intervention is being assessed than the answer should be NO if it is not widely available to the larger population			No	0

Internal validity - bias	14	Was an attempt made to blind study subjects to the intervention they had received? If question is not applicable then response should be NO			Yes	1
	15	Was an attempt made to blind those measuring the main outcomes of the interventions? If question is not applicable then response should be NO			Yes	1
	16	If any of the results of the study were based on "data dredging", was this made clear?			No	0
	17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? This should be answered NO if there is no follow-up and/or only 1 participant			Yes	1
	18	Were the statistical tests used to assess the main outcome appropriate?			Yes	1
	19	Was compliance with the intervention/s reliable? Single event studies should be answered NO, hopefully this will differentiate between studies who do have follow-ups and monitor compliance			Yes	1
	20	Were the main outcome measures used accurate (valid and reliable)? Technical papers should be considered valid and reliable if detailed explanation regarding equipment and protocol are included in the method			Yes	1

Internal validity - confounding (selection bias)	21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? Studies with no control group should score NO, if the study uses the intact leg as the control with unilateral amputee participants than score YES			Yes	1
	22	Were the study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? Studies with no control group should score NO, if the study uses the intact leg as the control with unilateral amputee participants than score YES			Yes	1
	23	Were the study subjects randomised to intervention groups?			Yes	1
	24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?			No	0
	25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? Single event studies should score NO			No	0
	26	Were losses of patients to follow-up taken into account? Studies with no follow-up should score NO			Yes	1
Power	**27**	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? This is still applicable for single group/single patient studies			**No**	**0**
Score						**21**

Comments	**Is the paper relevant to the project if there is limited general relevance?**	**Very Relevant**		
Overall Paper Quality	**Very good research design however poor statistics.**			

Paper Code		Lindenberg et al., (2010)				
		Participant Numbers (N) = 20		**>1**		
		Follow-Up?		**Yes**		
Downs and Black Questionnaire			**Comments**		**X**	**X Score**
Reporting	1	Is the hypothesis/aim/objective of the study clearly described?			No	0
	2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?			Yes	1
	3	Are the characteristics of the patients included in the study clearly described?			Yes	1
	4	Are the interventions of interest clearly described? Interventions have to be a comparison between equipment, protocol, rehab methods etc a one off measurement does not count			Yes	1
	5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?			Partially	1
	6	Are the main findings of the study clearly described?			Yes	1
	7	Does the study provide estimates of the random variability in the data for the main outcomes?			Yes	1
	8	Have all important adverse events that may be a consequence of the intervention been reported? For the paper to score yes the phrase "Adverse Events" has to be mentioned in the results/discussion/conclusion			Yes	1

	9	Have the characteristics of patients lost to follow-up been described? If there is no follow-up i.e. the study is just a single event study then the answer should be NO	.		No	1
	10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?			Yes	1
External validity	11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited? A single participant is not representative of the patient population as a whole			No	0
	12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?			No	0
	13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? This should be answered YES if you feel that the participants' treatment or care pathway, if stated, is similar to the larger population. If a novel or specialist intervention is being assessed than the answer should be NO if it is not widely available to the larger population			No	0
Internal validity - bias	14	Was an attempt made to blind study subjects to the intervention they had received? If question is not applicable then response should be NO			Yes	1
	15	Was an attempt made to blind those measuring the main outcomes of the interventions? If question is not applicable then response should be NO			Yes	1

	16	If any of the results of the study were based on "data dredging", was this made clear?			No	1
	17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? This should be answered NO if there is no follow-up and/or only 1 participant	.		Yes	0
	18	Were the statistical tests used to assess the main outcome appropriate?			No	1
	19	Was compliance with the intervention/s reliable? Single event studies should be answered NO, hopefully this will differentiate between studies who do have follow-ups and monitor compliance			No	1
	20	Were the main outcome measures used accurate (valid and reliable)? Technical papers should be considered valid and reliable if detailed explanation regarding equipment and protocol are included in the method			Yes	1
Internal validity - confounding (selection bias)	21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? Studies with no control group should score NO, if the study uses the intact leg as the control with unilateral amputee participants than score YES			No	0

	22	Were the study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? Studies with no control group should score NO, if the study uses the intact leg as the control with unilateral amputee participants than score YES			No	0
	23	Were the study subjects randomised to intervention groups?			No	1
	24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?			Yes	1
	25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? Single event studies should score NO			No	0
	26	Were losses of patients to follow-up taken into account? Studies with no follow-up should score NO			No	0
Power	27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? This is still applicable for single group/single patient studies			No	0
Score						**17**
Comments			**Is the paper relevant to the project if there is limited general relevance?**	**Very relevant**		
Overall Paper Quality			**Statistical analysis not clearly described**			

Paper Code		**Bolognini et al., (2011)**				
		Participant Numbers (N) = 14		**>1**		
		Follow-Up?		**Yes**		
Downs and Black Questionnaire			**Comments**		**X**	**X Score**
Reporting	1	Is the hypothesis/aim/objective of the study clearly described?			Yes	1
	2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?			Yes	1
	3	Are the characteristics of the patients included in the study clearly described?			Yes	1
	4	Are the interventions of interest clearly described? Interventions have to be a comparison between equipment, protocol, rehab methods etc a one off measurement does not count			Yes	1
	5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?			Partially	1
	6	Are the main findings of the study clearly described?			Yes	1
	7	Does the study provide estimates of the random variability in the data for the main outcomes?			Yes	1
	8	Have all important adverse events that may be a consequence of the intervention been reported? For the paper to score yes the phrase "Adverse Events" has to be mentioned in the results/discussion/conclusion			Yes	1

	9	Have the characteristics of patients lost to follow-up been described? If there is no follow-up i.e. the study is just a single event study then the answer should be NO			No	0
	10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?			Yes	1
External validity	11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited? A single participant is not representative of the patient population as a whole			No	0
	12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?			No	0
	13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? This should be answered YES if you feel that the participants' treatment or care pathway, if stated, is similar to the larger population. If a novel or specialist intervention is being assessed than the answer should be NO if it is not widely available to the larger population			No	0

Internal validity - bias	14	Was an attempt made to blind study subjects to the intervention they had received? If question is not applicable then response should be NO			Yes	1
	15	Was an attempt made to blind those measuring the main outcomes of the interventions? If question is not applicable then response should be NO			Yes	1
	16	If any of the results of the study were based on "data dredging", was this made clear?			Yes	1
	17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? This should be answered NO if there is no follow-up and/or only 1 participant			No	0
	18	Were the statistical tests used to assess the main outcome appropriate?			Yes	1
	19	Was compliance with the intervention/s reliable? Single event studies should be answered NO, hopefully this will differentiate between studies who do have follow-ups and monitor compliance			No	1
	20	Were the main outcome measures used accurate (valid and reliable)? Technical papers should be considered valid and reliable if detailed explanation regarding equipment and protocol are			Yes	1

		included in the method				
Internal validity - confounding (selection bias)	21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? Studies with no control group should score NO, if the study uses the intact leg as the control with unilateral amputee participants than score YES			No	0
	22	Were the study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? Studies with no control group should score NO, if the study uses the intact leg as the control with unilateral amputee participants than score YES			No	0
	23	Were the study subjects randomised to intervention groups?			Yes	1
	24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?			No	0
	25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? Single event studies should score NO			No	0
	26	Were losses of patients to follow-up taken into account? Studies with no follow-up should score NO			No	0

Power	27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? This is still applicable for single group/single patient studies			No	0
Score						**16**
Comments			Is the paper relevant to the project if there is limited general relevance?	**Very relevant using CIMT and tdcs**		
Overall Paper Quality			**Very good quality**			

Paper Code		Hesse et al. 2011				
		Participant Numbers (N) = 96		>1		
		Follow-Up? 3 month		Yes		
Downs and Black Questionnaire			**Comments**		**X**	**X Score**
Reporting	1	Is the hypothesis/aim/objective of the study clearly described?			Yes	1
	2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?			Yes	1
	3	Are the characteristics of the patients included in the study clearly described?			Yes	1
	4	Are the interventions of interest clearly described? Interventions have to be a comparison between equipment, protocol, rehab methods etc a one off measurement does not count			Yes	1
	5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?			Yes	2
	6	Are the main findings of the study clearly described?			Yes	1
	7	Does the study provide estimates of the random variability in the data for the main outcomes?			Yes	1

	8	Have all important adverse events that may be a consequence of the intervention been reported? For the paper to score yes the phrase "Adverse Events" has to be mentioned in the results/discussion/conclusion			Yes	1
	9	Have the characteristics of patients lost to follow-up been described? If there is no follow-up ie the study is just a single event study then the answer should be NO	.		Yes	1
	10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?			Yes	1
External validity	11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited? A single participant is not representative of the patient population as a whole			No	0
	12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?			No	0

	13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? This should be answered YES if you feel that the participants' treatment or care pathway, if stated, is similar to the larger population. If a novel or specialist intervention is being assessed than the answer should be NO if it is not widely available to the larger population			No	0
Internal validity - bias	14	Was an attempt made to blind study subjects to the intervention they had received? If question is not applicable then response should be NO			Yes	1
	15	Was an attempt made to blind those measuring the main outcomes of the interventions? If question is not applicable then response should be NO			Yes	1
	16	If any of the results of the study were based on "data dredging", was this made clear?			No	0
	17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? This should be answered NO if there is no follow-up and/or only 1 participant	.		Yes	1

	18	Were the statistical tests used to assess the main outcome appropriate?			Yes	1
	19	Was compliance with the intervention/s reliable? Single event studies should be answered NO, hopefully this will differentiate between studies who do have follow-ups and monitor compliance			Yes	1
	20	Were the main outcome measures used accurate (valid and reliable)? Technical papers should be considered valid and reliable if detailed explanation regarding equipment and protocol are included in the method			Yes	1
Internal validity - confounding (selection bias)	21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? Studies with no control group should score NO, if the study uses the intact leg as the control with unilateral amputee participants than score YES			No	0
	22	Were the study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? Studies with no control group should score NO, if the study uses the intact leg as the control			No	0

		with unilateral amputee participants than score YES				
	23	Were the study subjects randomised to intervention groups?			Yes	1
	24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?			Yes	1
	25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? Single event studies should score NO			Yes	1
	26	Were losses of patients to follow-up taken into account? Studies with no follow-up should score NO			Yes	1
Power	27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? This is still applicable for single group/single patient studies			Yes	1
Score						**22**
Comments			Is the paper relevant to the project if there is limited general relevance?	**Very relevant study similar to our protocol**		
Overall Paper Quality			**Bi manu track; 20 min RT during training**			

Paper Code		**Nair et al., 2011**				
		Participant Numbers (N) = 14		**>1**		
		Follow-Up?		**Yes**		
Downs and Black Questionnaire			**Comments**		**X**	**X Score**
Reporting	1	Is the hypothesis/aim/objective of the study clearly described?			Yes	1
	2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?			Yes	1
	3	Are the characteristics of the patients included in the study clearly described?			Yes	1
	4	Are the interventions of interest clearly described? Interventions have to be a comparison between equipment, protocol, rehab methods etc a one off measurement does not count			Yes	1
	5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?			Yes	1
	6	Are the main findings of the study clearly described?			Yes	1
	7	Does the study provide estimates of the random variability in the data for the main outcomes?			Yes	1

	8	Have all important adverse events that may be a consequence of the intervention been reported? For the paper to score yes the phrase "Adverse Events" has to be mentioned in the results/discussion/conclusion			No	0
	9	Have the characteristics of patients lost to follow-up been described? If there is no follow-up ie the study is just a single event study then the answer should be NO	.		No	0
	10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?			Yes	1
External validity	11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited? A single participant is not representative of the patient population as a whole			No	0
	12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?			No	0

	13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? This should be answered YES if you feel that the participants' treatment or care pathway, if stated, is similar to the larger population. If a novel or specialist intervention is being assessed than the answer should be NO if it is not widely available to the larger population			No	0
Internal validity - bias	14	Was an attempt made to blind study subjects to the intervention they had received? If question is not applicable then response should be NO			Yes	1
	15	Was an attempt made to blind those measuring the main outcomes of the interventions? If question is not applicable then response should be NO			Yes	1
	16	If any of the results of the study were based on "data dredging", was this made clear?			Yes	1
	17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? This should be answered NO if there is no follow-up and/or only 1 participant	.		No	0

	18	Were the statistical tests used to assess the main outcome appropriate?			Yes	1
	19	Was compliance with the intervention/s reliable? Single event studies should be answered NO, hopefully this will differentiate between studies who do have follow-ups and monitor compliance			Yes	1
	20	Were the main outcome measures used accurate (valid and reliable)? Technical papers should be considered valid and reliable if detailed explanation regarding equipment and protocol are included in the method			Yes	1
Internal validity - confoundin g (selection bias)	21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? Studies with no control group should score NO, if the study uses the intact leg as the control with unilateral amputee participants than score YES			No	0
	22	Were the study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? Studies with no control group should score NO, if the study uses the intact leg as the control			No	0

		with unilateral amputee participants than score YES				
	23	Were the study subjects randomised to intervention groups?			Yes	1
	24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?			Yes	1
	25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? Single event studies should score NO			Yes	0
	26	Were losses of patients to follow-up taken into account? Studies with no follow-up should score NO			Yes	1
Power	27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? This is still applicable for single group/single patient studies			No	0
Score						**17**
Comments			Is the paper relevant to the project if there is limited general relevance?	**Relevant study**		
Overall Paper Quality			**Good quality however inconsistent presentation of statistics**			

Paper Code		**<u>Ochi et al., 2013</u>**				
		Participant Numbers (N) = 18		**>1**		
		Follow-Up?		**No**		
Downs and Black Questionnaire			**Comments**		**X**	**X Score**
Reporting	1	Is the hypothesis/aim/objective of the study clearly described?			Yes	1
	2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?			Yes	1
	3	Are the characteristics of the patients included in the study clearly described?			Yes	1
	4	Are the interventions of interest clearly described? Interventions have to be a comparison between equipment, protocol, rehab methods etc a one off measurement does not count			No	1
	5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?			Yes	1
	6	Are the main findings of the study clearly described?			Yes	1
	7	Does the study provide estimates of the random variability in the data for the main outcomes?			Yes	1

	8	Have all important adverse events that may be a consequence of the intervention been reported? For the paper to score yes the phrase "Adverse Events" has to be mentioned in the results/discussion/conclusion			Yes	1
	9	Have the characteristics of patients lost to follow-up been described? If there is no follow-up ie the study is just a single event study then the answer should be NO	.		No	0
	10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?			Yes	1
External validity	11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited? A single participant is not representative of the patient population as a whole			No	0
	12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?			No	0

	13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? This should be answered YES if you feel that the participants' treatment or care pathway, if stated, is similar to the larger population. If a novel or specialist intervention is being assessed than the answer should be NO if it is not widely available to the larger population			No	0
Internal validity - bias	14	Was an attempt made to blind study subjects to the intervention they had received? If question is not applicable then response should be NO			No	0
	15	Was an attempt made to blind those measuring the main outcomes of the interventions? If question is not applicable then response should be NO			Yes	1
	16	If any of the results of the study were based on "data dredging", was this made clear?			No	0
	17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? This should be answered NO if there is no follow-up and/or only 1 participant	.		No	0

	18	Were the statistical tests used to assess the main outcome appropriate?			Yes	1
	19	Was compliance with the intervention/s reliable? Single event studies should be answered NO, hopefully this will differentiate between studies who do have follow-ups and monitor compliance			Yes	1
	20	Were the main outcome measures used accurate (valid and reliable)? Technical papers should be considered valid and reliable if detailed explanation regarding equipment and protocol are included in the method			Yes	1
Internal validity - confounding (selection bias)	21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? Studies with no control group should score NO, if the study uses the intact leg as the control with unilateral amputee participants than score YES			No	0
	22	Were the study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? Studies with no control group should score NO, if the study uses the intact leg as the control			No	0

		with unilateral amputee participants than score YES				
	23	Were the study subjects randomised to intervention groups?			No	0
	24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?			No	0
	25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? Single event studies should score NO			No	0
	26	Were losses of patients to follow-up taken into account? Studies with no follow-up should score NO			No	0
Power	27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? This is still applicable for single group/single patient studies			No	0
Score						
Comments			**Is the paper relevant to the project if there is limited general relevance?**	**Relevant**		
Overall Paper Quality			**Very good quality**			

Paper Code		Khedr et al., 2013				
		Participant Numbers (N) = 40		**>1**		
		Follow-Up?		**Yes**		
Downs and Black Questionnaire			**Comments**		**X**	**X Score**
Reporting	1	Is the hypothesis/aim/objective of the study clearly described?			Yes	1
	2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?			Yes	1
	3	Are the characteristics of the patients included in the study clearly described?			Yes	1
	4	Are the interventions of interest clearly described? Interventions have to be a comparison between equipment, protocol, rehab methods etc a one off measurement does not count			No	1
	5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?			Yes	1
	6	Are the main findings of the study clearly described?			Yes	1
	7	Does the study provide estimates of the random variability in the data for the main outcomes?			Yes	1

	8	Have all important adverse events that may be a consequence of the intervention been reported? For the paper to score yes the phrase "Adverse Events" has to be mentioned in the results/discussion/conclusion			Yes	1
	9	Have the characteristics of patients lost to follow-up been described? If there is no follow-up ie the study is just a single event study then the answer should be NO	.		Yes	1
	10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?			Yes	1
External validity	11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited? A single participant is not representative of the patient population as a whole			Yes	1
	12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?			No	1

	13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? This should be answered YES if you feel that the participants' treatment or care pathway, if stated, is similar to the larger population. If a novel or specialist intervention is being assessed than the answer should be NO if it is not widely available to the larger population			No	1
Internal validity - bias	14	Was an attempt made to blind study subjects to the intervention they had received? If question is not applicable then response should be NO			Yes	1
	15	Was an attempt made to blind those measuring the main outcomes of the interventions? If question is not applicable then response should be NO			Yes	1
	16	If any of the results of the study were based on "data dredging", was this made clear?			Yes	1
	17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? This should be answered NO if there is no follow-up and/or only 1 participant	.		Yes	1

	18	Were the statistical tests used to assess the main outcome appropriate?			Yes	1
	19	Was compliance with the intervention/s reliable? Single event studies should be answered NO, hopefully this will differentiate between studies who do have follow-ups and monitor compliance			Yes	1
	20	Were the main outcome measures used accurate (valid and reliable)? Technical papers should be considered valid and reliable if detailed explanation regarding equipment and protocol are included in the method			Yes	1
Internal validity - confounding (selection bias)	21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? Studies with no control group should score NO, if the study uses the intact leg as the control with unilateral amputee participants than score YES			Yes	1
	22	Were the study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? Studies with no control group should score NO, if the study uses the intact leg as the control			Yes	1

		with unilateral amputee participants than score YES				
	23	Were the study subjects randomised to intervention groups?			Yes	1
	24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?			Yes	1
	25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? Single event studies should score NO			No	0
	26	Were losses of patients to follow-up taken into account? Studies with no follow-up should score NO			Yes	1
Power	27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? This is still applicable for single group/single patient studies			No	1
Score						**25**
Comments			**Is the paper relevant to the project if there is limited general relevance?**	**Relevant**		
Overall Paper Quality			**Very good quality**			

Paper Code		**<u>Wu et al., 2013</u>**				
		Participant Numbers (N) = 90		**>1**		
		Follow-Up?		**Yes**		
Downs and Black Questionnaire			**Comments**		**X**	**X Score**
Reporting	1	Is the hypothesis/aim/objective of the study clearly described?			Yes	1
	2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?			Yes	1
	3	Are the characteristics of the patients included in the study clearly described?			Yes	1
	4	Are the interventions of interest clearly described? Interventions have to be a comparison between equipment, protocol, rehab methods etc a one off measurement does not count			No	0
	5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?			Yes	1
	6	Are the main findings of the study clearly described?			Yes	1
	7	Does the study provide estimates of the random variability in the data for the main outcomes?			Yes	1

	8	Have all important adverse events that may be a consequence of the intervention been reported? For the paper to score yes the phrase "Adverse Events" has to be mentioned in the results/discussion/conclusion			Yes	1
	9	Have the characteristics of patients lost to follow-up been described? If there is no follow-up ie the study is just a single event study then the answer should be NO	.		Yes	1
	10	Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?			Yes	1
External validity	11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited? A single participant is not representative of the patient population as a whole			Yes	1
	12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?			No	0

	13	Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? This should be answered YES if you feel that the participants' treatment or care pathway, if stated, is similar to the larger population. If a novel or specialist intervention is being assessed than the answer should be NO if it is not widely available to the larger population			No	1
Internal validity - bias	14	Was an attempt made to blind study subjects to the intervention they had received? If question is not applicable then response should be NO			Yes	1
	15	Was an attempt made to blind those measuring the main outcomes of the interventions? If question is not applicable then response should be NO			Yes	1
	16	If any of the results of the study were based on "data dredging", was this made clear?			Yes	1
	17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? This should be answered NO if there is no follow-up and/or only 1 participant	.		Yes	1

	18	Were the statistical tests used to assess the main outcome appropriate?			Yes	1
	19	Was compliance with the intervention/s reliable? Single event studies should be answered NO, hopefully this will differentiate between studies who do have follow-ups and monitor compliance			Yes	1
	20	Were the main outcome measures used accurate (valid and reliable)? Technical papers should be considered valid and reliable if detailed explanation regarding equipment and protocol are included in the method			Yes	1
Internal validity - confounding (selection bias)	21	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? Studies with no control group should score NO, if the study uses the intact leg as the control with unilateral amputee participants than score YES			Yes	1
	22	Were the study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? Studies with no control group should score NO, if the study uses the intact leg as the control			Yes	1

		with unilateral amputee participants than score YES				
	23	Were the study subjects randomised to intervention groups?			Yes	1
	24	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?			Yes	1
	25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? Single event studies should score NO			Yes	0
	26	Were losses of patients to follow-up taken into account? Studies with no follow-up should score NO			Yes	1
Power	27	Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? This is still applicable for single group/single patient studies			No	0
Score						**24**
Comments			**Is the paper relevant to the project if there is limited general relevance?**	**Relevant**		
Overall Paper Quality			**Very good quality**			

Appendix B

Information Packs

B.1 Information pack-Randomised controlled trial

B.1.1 Participant invitation letter

Date: 27.07.11
Ethics Number: 11/SC/0345
Version 1

Dear Sir/Madam,

We would like to invite you to participate in our Physiotherapy research project at the University of Southampton.

We are carrying out a study to test whether non-invasive brain stimulation can improve moving your arm and hand. If you are able to and are happy to take part, you will be invited to attend our Movement Laboratory at the University of Southampton on twenty occasions.

At the Movement Laboratory, we will make use of a robotic device where your arm and hand is positioned in. This is painless and you will still be able to move your arm and hand. In front of you, there will be a computer screen and by moving your arm and hand, you will be able to play games on this computer screen. After a series of games, we will apply the non-invasive brain stimulation. This will be two square, wet patches that will be positioned on your head. The non-invasive brain stimulation is painless but can provide a minimal discomfort such as tingling or itching under the patches. After the application of brain stimulation, we will measure how well you score on the games you play.

I am writing to ask if you would be willing to participate in this study. Attached to this letter is an information sheet that explains in more detail what the study involves. If you have any questions that are not answered in the information sheet you are very welcome to phone us on 02380595297 or e-mail ltt1g09@soton.ac.uk.

If, having read the information sheet, you are interested in taking part in the study; I would be very grateful if you could complete the attached reply slip and return it in the envelope provided.

Thank you,

Yours faithfully

Lisa Tedesco Triccas
Research Fellow University of Southampton

B.1.2 Participant information sheet- Version 2

Date: 14.09.11

Ethics Number: 11/SC/0345

Version 2

Combining brain stimulation with robot therapy for the impaired arm in early stroke rehabilitation

Our names are Lisa Tedesco Triccas, Professor Jane Burridge and Dr Ann-Marie Hughes. We are researchers at the University of Southampton specialising in rehabilitation of people with stroke. We are writing to invite you to take part in a research study that is part of doctoral degree.

It is important for you to understand why the research is being carried out and what it will involve before you decide whether to take part. Please take your time to read the following information carefully and discuss it with friends, relatives, and your GP if you wish. If something is not clear, or you would like further information, please do not hesitate to contact us at the address or telephone number given at the end of this information sheet.

Thank you for reading this.

What is the purpose of this study?

People with stroke often experience difficulties moving their arm. Two new technologies that may assist recovery of arm movement, when used as part of conventional rehabilitation, are non-invasive brain stimulation and rehabilitation robot therapy. Both brain stimulation and robot therapy have been shown, in preliminary research, to be of benefit. This study will test whether combining brain stimulation and robot therapy is any more effective than robot therapy alone.

Why have I been chosen?

We would like 50 people who had a stroke affecting their arm to take part in the study. You have been identified as a possible participant.

Do I have to take part?

You do not have to take part in the study. If you decide to take part you are 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 rights or the care you receive.

What will happen to me if I take part?

If you return the attached form saying you are interested in taking part you will be contacted by telephone or in person by one of the researchers. This person will come and discuss the study with you either on the hospital ward or at your home and will answer any questions you might have. If, after this, you would like to take part, an appointment will be made for you to come to the Movement Laboratory at the University. Transport will be provided.

At the laboratory, the researcher (who is a qualified physiotherapist) will ask you to give written informed consent to taking part. They will also ask for your consent to be photographed and for videos to be taken while you are using the robot. These are for research and education purpose and you do not need to consent to this to take part in the study. You will then be assessed to ensure you satisfy the criteria for taking part in the study. This will involve asking you questions about your condition and assessing your affected arm and hand. If you satisfy the criteria you will be able start on the study straight away.

The study involves two groups. One group will receive 'real' non-invasive brain stimulation and robot therapy while the other group will be receiving 'placebo' or 'sham' stimulation. You will be placed in one of the two groups by random selection.

Taking part will mean attending 19 sessions (including the first session) at the Movement Laboratory of the University of Southampton. Each visit will last for about an hour and a half. The first 18 sessions will be carried out within 8 weeks and the last (19^{th}) session will be carried out three months after the treatment has been completed.

Visits to the Movement Laboratory:

On arrival the researcher will meet you, show you the equipment and explain the procedures. You will be invited to sit in a chair with a back support. The researcher will position two electrodes (patches) on your head that transmit the low-level (1mA) electric current, (trans-cranial direct current stimulation). Your affected arm and hand will then be positioned in the robot, the support it gives will make it feel less heavy. In front of you, there will be a computer screen that is connected to the robotic device. By moving your arm, you will be able to play games, shown on the computer screen. Once you are comfortable, the stimulator is switched on and you will be asked to perform a set of games for an hour, taking as many rests as often as you like. If you are in the 'sham' group the stimulator will be turned off after one minute; if you are in the 'real stimulation' group it will stay on for 20 minutes. Because you will not feel anything after the first few seconds of stimulation you will not know which group you are in.

Assessments will be done on your first visit, at the end of your 18^{th} session and three months following the 18th session. The assessments will involve measurements of movements and activities carried out by your affected arm. We will also test the nerve connections between your brain and your affected arm and hand using Transcranial Magnetic Stimulation. This device, which is held above your head, sends a small pulse from your brain to the muscles in your arm and hand. By measuring the response in your muscles we can tell how good the connections are.

You can bring along a friend or family member with you to all the sessions. Refreshments will be provided and travel expenses (mileage and parking fee or taxi fare) will be reimbursed. You will be asked to wear loose fitting, comfortable clothing.

What kind of personal information is needed and how is it going to be used?

Your consultant, researcher or research nurse may inspect your medical records, but all information they obtain will be coded by a unique identifier (ID) to ensure it is kept confidential.

What are the possible benefits of taking part?

We do not know whether you will benefit from taking part in this study. However, we expect that the results of the study will inform researchers working in the field of stroke rehabilitation, assisting progress towards new strategies for treating the arm and hand.

What are the side effects of taking part?

During robot therapy, you might feel tired. You will be asked throughout the session how you are feeling and will be able to take breaks whenever you like.

Brain stimulation is painless but can produce minor discomfort; for instance, some people feel a tingling or itching sensation under the patches when the stimulator is turned on. Some people notice redness of the skin under the patches when they are removed. Rarely, people have reported a slight headache and light flashes in front of the eyes when the stimulator is turned on or off, sleepiness, mood changes, drowsiness, concentration problems or burning of the skin. When using Transcranial Magnetic Stimulation, there have been reports of people experiencing an epileptic seizure, headache, neck pain, toothache, slight problems with sensation and hearing changes but this is highly unlikely.

We do not anticipate any of these rare side effects as our protocol adheres to the current safety guidelines. We will monitor you closely throughout the visit and ask you to report any discomfort you experience which might be related to the study. If at any point you feel unwell you may rest. If you feel unable to continue you may withdraw. A physiotherapy researcher will be close to you to ensure you are safe at all times.

What if something goes wrong?

If you have a concern or a complaint about this study you should contact Zena Galbraith (Z.Galbraith@soton.ac.uk) at the Health Sciences Faculty Research Office, University of Southampton, Building 67, Highfield, Southampton, SO17 1BJ; Tel: 023 8059 7942. If you remain unhappy and wish to complain formally Zena Galbraith will provide you with details of the University of Southampton Complaints Procedure.

What if new information about risks or side effects becomes available during the study?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the research physiotherapist will inform you about it and discuss with you whether you want to continue taking part in the study.

Who is organising the research & reviewing the study?

The study is being run by the University of Southampton and has been reviewed by a National Health Service (NHS) Research Ethics Committee.

What will happen to the results of the research?

At the end of the research, the data collected will be securely stored at the University of Southampton for 10 years. The results will be presented at conferences and will be published in research papers for scientific journals. We hope this will help to inform clinicians of the results and improve the treatment of patients. We will send you a lay summary of our findings at the end of the study if you wish. If you would like a copy of the published results please let us know.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that is used in research reports, publications or presentations will refer only to your study ID. Any photographs or videos will be made anonymous by blurring or obscuring your face.

Contact for further information:

If you would like more information please contact Ms. Lisa Tedesco Triccas on 02380 595297 or email ltt1g09@soton.ac.uk.

Thank you once again for taking the time to read this information.

B.1.3 Participant information sheet- Version 3

Date: 23.05.12

Ethics Number: 11/SC/0345

Version 3

Combining brain stimulation with robot therapy for the impaired arm in early stroke rehabilitation

Our names are Lisa Tedesco Triccas, Professor Jane Burridge and Dr Ann-Marie Hughes. We are researchers at the University of Southampton specialising in rehabilitation of people with stroke. We are writing to invite you to take part in a research study that is part of doctoral degree.

It is important for you to understand why the research is being carried out and what it will involve before you decide whether to take part. Please take your time to read the following information carefully and discuss it with friends, relatives, and your GP if you wish. If something is not clear, or you would like further information, please do not hesitate to contact us at the address or telephone number given at the end of this information sheet.

Thank you for reading this.

What is the purpose of this study?

People with stroke often experience difficulties moving their arm. Two new technologies that may assist recovery of arm movement, when used as part of conventional rehabilitation, are non-invasive brain stimulation and rehabilitation robot therapy. Both brain stimulation and robot therapy have been shown, in preliminary research, to be of benefit. This study will test whether combining brain stimulation and robot therapy is any more effective than robot therapy alone.

Why have I been chosen?

We would like 50 people who had a stroke affecting their arm to take part in the study. You have been identified as a possible participant.

Do I have to take part?

You do not have to take part in the study. If you decide to take part you are 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 rights or the care you receive.

What will happen to me if I take part?

If you return the attached form saying you are interested in taking part you will be contacted by telephone or in person by one of the researchers. This person will come and discuss the study with you either on the hospital ward or at your home and will answer any questions you might have. If, after this, you would like to take part, an appointment will be made for you to come to the Movement Laboratory at the University. Transport will be provided.

At the laboratory, the researcher (who is a qualified physiotherapist) will ask you to give written informed consent to taking part. They will also ask for your consent to be photographed and for videos to be taken while you are using the robot. These are for research and education purpose and you do not need to consent to this to take part in the study. You will then be assessed to ensure you satisfy the criteria for taking part in the study. This will involve asking you questions about your condition and assessing your affected arm and hand. If you satisfy the criteria you will be able start on the study straight away.

The study involves two groups. One group will receive ‘real’ non-invasive brain stimulation and robot therapy while the other group will be receiving ‘placebo’ or ‘sham’ stimulation. You will be placed in one of the two groups by random selection.

Taking part will mean attending 19 sessions (including the first session) at the Movement Laboratory of the University of Southampton. Each visit will last for about an hour and a half. The first 18 sessions will be carried out within 8 weeks and the last (19^{th}) session will be carried out three months after the treatment has been completed. **In addition after completing the research study and if you give additional consent, an informal interview will take place at your home. An independent researcher will visit you and questions will be asked about your experiences and views of taking part in this research.**

Visits to the Movement Laboratory:

On arrival the researcher will meet you, show you the equipment and explain the procedures. You will be invited to sit in a chair with a back support. The researcher will position two electrodes (patches) on your head that transmit the low-level (1mA) electric current, (trans-cranial direct current stimulation). Your affected arm and hand will then be positioned in the robot, the support it gives will make it feel less heavy. In front of you, there will be a computer screen that is connected to the robotic device. By moving your arm, you will be able to play games, shown on the computer screen. Once you are comfortable, the stimulator is switched on and you will be asked to perform a set of games for an hour, taking as many rests as often as you like. If you are in the ‘sham’ group the stimulator will be turned off after one minute; if you are in the ‘real stimulation’ group it will stay on for 20 minutes. Because you will not feel anything after the first few seconds of stimulation you will not know which group you are in.

Assessments will be done on your first visit, at the end of your 18^{th} session and three months following the 18th session. The assessments will involve measurements of movements and activities carried out by your affected arm. We will also test the nerve connections between your brain and your affected arm and hand using Transcranial Magnetic Stimulation. This device, which is held above your head, sends a small pulse from your brain to the muscles in your arm and hand. By measuring the response in your muscles we can tell how good the connections are.

You can bring along a friend or family member with you to all the sessions. Refreshments will be provided and travel expenses (mileage and parking fee or taxi fare) will be reimbursed. You will be asked to wear loose fitting, comfortable clothing.

What kind of personal information is needed and how is it going to be used?

Your consultant, researcher or research nurse may inspect your medical records, but all information they obtain will be coded by a unique identifier (ID) to ensure it is kept confidential.

What are the possible benefits of taking part?

We do not know whether you will benefit from taking part in this study. However, we expect that the results of the study will inform researchers working in the field of stroke rehabilitation, assisting progress towards new strategies for treating the arm and hand.

What are the side effects of taking part?

During robot therapy, you might feel tired. You will be asked throughout the session how you are feeling and will be able to take breaks whenever you like.

Brain stimulation is painless but can produce minor discomfort; for instance, some people feel a tingling or itching sensation under the patches when the stimulator is turned on. Some people notice redness of the skin under the patches when they are removed. Rarely, people have reported a slight headache and light flashes in front of the eyes when the stimulator is turned on or off, sleepiness, mood changes, drowsiness, concentration problems or burning of the skin. When using Transcranial Magnetic Stimulation, there have been reports of people experiencing an epileptic seizure, headache, neck pain, toothache, slight problems with sensation and hearing changes but this is highly unlikely.

We do not anticipate any of these rare side effects as our protocol adheres to the current safety guidelines. We will monitor you closely throughout the visit and ask you to report any discomfort you experience which might be related to the study. If at any point you feel unwell you may rest. If you feel unable to continue you may withdraw. A physiotherapy researcher will be close to you to ensure you are safe at all times.

What if something goes wrong?

If you have a concern or a complaint about this study you should contact Zena Galbraith (Z.Galbraith@soton.ac.uk) at the Health Sciences Faculty Research Office, University of Southampton, Building 67, Highfield, Southampton, SO17 1BJ; Tel: 023 8059 7942. If you remain unhappy and wish to complain formally

Zena Galbraith will provide you with details of the University of Southampton Complaints Procedure.

What if new information about risks or side effects becomes available during the study?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the research physiotherapist will inform you about it and discuss with you whether you want to continue taking part in the study.

Who is organising the research & reviewing the study?

The study is being run by the University of Southampton and has been reviewed by a National Health Service (NHS) Research Ethics Committee.

What will happen to the results of the research?

At the end of the research, the data collected will be securely stored at the University of Southampton for 10 years. The results will be presented at conferences and will be published in research papers for scientific journals. We hope this will help to inform clinicians of the results and improve the treatment of patients. We will send you a lay summary of our findings at the end of the study if you wish. If you would like a copy of the published results please let us know.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that is used in research reports, publications or presentations will refer only to your study ID. Any photographs or videos will be made anonymous by blurring or obscuring your face.

Contact for further information:

If you would like more information please contact Ms. Lisa Tedesco Triccas on 02380 595297 or email ltt1g09@soton.ac.uk.

Thank you once again for taking the time to read this information.

B.1.4 Participant information sheet- Version 4

Date: 17.01.13
Ethics Number: 11/SC/0345
Version 4

Combining brain stimulation with robot therapy for the impaired arm in early stroke rehabilitation

Our names are Lisa Tedesco Triccas, Professor Jane Burridge and Dr Ann-Marie Hughes. We are researchers at the University of Southampton specialising in rehabilitation of people with stroke. We are writing to invite you to take part in a research study that is part of doctoral degree.

It is important for you to understand why the research is being carried out and what it will involve before you decide whether to take part. Please take your time to read the following information carefully and discuss it with friends, relatives, and your GP if you wish. If something is not clear, or you would like further information, please do not hesitate to contact us at the address or telephone number given at the end of this information sheet.

Thank you for reading this.

What is the purpose of this study?

People with stroke often experience difficulties moving their arm. Two new technologies that may assist recovery of arm movement, when used as part of conventional rehabilitation, are non-invasive brain stimulation and rehabilitation robot therapy. Both brain stimulation and robot therapy have been shown, in preliminary research, to be of benefit. This study will test whether combining brain stimulation and robot therapy is any more effective than robot therapy alone.

Why have I been chosen?

We would like 50 people who had a stroke affecting their arm to take part in the study. You have been identified as a possible participant.

Do I have to take part?

You do not have to take part in the study. If you decide to take part you are 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 rights or the care you receive.

What will happen to me if I take part?

If you return the attached form saying you are interested in taking part you will be contacted by telephone or in person by one of the researchers. This person will come and discuss the study with you either on the hospital ward or at your home and will answer any questions you might have. If, after this, you would like to take part, an appointment will be made for you to come to the Movement Laboratory at the University. Transport will be provided.

At the laboratory, the researcher (who is a qualified physiotherapist) will ask you to give written informed consent to taking part. They will also ask for your consent to be photographed and for videos to be taken while you are using the robot. These are for research and education purpose and you do not need to consent to this to take part in the study. You will then be assessed to ensure you satisfy the criteria for taking part in the study. This will involve asking you questions about your condition and assessing your affected arm and hand. If you satisfy the criteria you will be able start on the study straight away.

The study involves two groups. One group will receive ‘real’ non-invasive brain stimulation and robot therapy while the other group will be receiving ‘placebo’ or ‘sham’ stimulation. You will be placed in one of the two groups by random selection.

Taking part will mean attending 19-20 sessions. The first and last session (assessment) will take place at the Movement Laboratory of the University of Southampton the rest of the sessions will take place at Christchurch hospital. Each visit will last for about an hour and a half. The first 18 sessions will be carried out within 8 weeks and the last session will be carried out three months after the treatment has been completed. In addition after completing the research study and if you give additional consent, an informal interview will take place at your home. An independent researcher will visit you and questions will be asked about your experiences and views of taking part in this research.

Visits to the Movement Laboratory or the hospital:

On arrival the researcher will meet you, show you the equipment and explain the procedures. You will be invited to sit in a chair with a back support. The researcher will position two electrodes (patches) on your head that transmit the low-level (1mA) electric current, (trans-cranial direct current stimulation). Your affected arm and hand will then be positioned in the robot, the support it gives will make it feel less heavy. In front of you, there will be a computer screen that is connected to the robotic device. By moving your arm, you will be able to play games, shown on the computer screen. Once you are comfortable, the stimulator is switched on and you will be asked to perform a set of games for an hour, taking as many rests as often as you like. If you are in the 'sham' group the stimulator will be turned off after one minute; if you are in the 'real stimulation' group it will stay on for 20 minutes. Because you will not feel anything after the first few seconds of stimulation you will not know which group you are in.

Assessments will be done on your first visit, at the end of your 18^{th} session and three months following the 18th session. The assessments will involve measurements of movements and activities carried out by your affected arm. We will also test the nerve connections between your brain and your affected arm and hand using Transcranial Magnetic Stimulation. This device, which is held above your head, sends a small pulse from your brain to the muscles in your arm and hand. By measuring the response in your muscles we can tell how good the connections are.

You can bring along a friend or family member with you to all the sessions. Refreshments will be provided and travel expenses (mileage and parking fee or taxi fare) will be reimbursed. You will be asked to wear loose fitting, comfortable clothing.

0What kind of personal information is needed and how is it going to be used?

Your consultant, researcher or research nurse may inspect your medical records, but all information they obtain will be coded by a unique identifier (ID) to ensure it is kept confidential.

What are the possible benefits of taking part?

We do not know whether you will benefit from taking part in this study. However, we expect that the results of the study will inform researchers working in the field of stroke rehabilitation, assisting progress towards new strategies for treating the arm and hand.

What are the side effects of taking part?

During robot therapy, you might feel tired. You will be asked throughout the session how you are feeling and will be able to take breaks whenever you like.

Brain stimulation is painless but can produce minor discomfort; for instance, some people feel a tingling or itching sensation under the patches when the stimulator is turned on. Some people notice redness of the skin under the patches when they are removed. Rarely, people have reported a slight headache and light flashes in front of the eyes when the stimulator is turned on or off, sleepiness, mood changes, drowsiness, concentration problems or burning of the skin. When using Transcranial Magnetic Stimulation, there have been reports of people experiencing an epileptic seizure, headache, neck pain, toothache, slight problems with sensation and hearing changes but this is highly unlikely.

We do not anticipate any of these rare side effects as our protocol adheres to the current safety guidelines. We will monitor you closely throughout the visit and ask you to report any discomfort you experience which might be related to the study. If at any point you feel unwell you may rest. If you feel unable to continue you may withdraw. A physiotherapy researcher will be close to you to ensure you are safe at all times.

What if something goes wrong?

If you have a concern or a complaint about this study you should contact Zena Galbraith (Z.Galbraith@soton.ac.uk) at the Health Sciences Faculty Research Office, University of Southampton, Building 67, Highfield, Southampton, SO17 1BJ; Tel: 023 8059 7942. If you remain unhappy and wish to complain formally Zena Galbraith will provide you with details of the University of Southampton Complaints Procedure.

What if new information about risks or side effects becomes available during the study?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the research physiotherapist will inform you about it and discuss with you whether you want to continue taking part in the study.

Who is organising the research & reviewing the study?

The study is being run by the University of Southampton and has been reviewed by a National Health Service (NHS) Research Ethics Committee.

What will happen to the results of the research?

At the end of the research, the data collected will be securely stored at the University of Southampton for 10 years. The results will be presented at conferences and will be published in research papers for scientific journals. We hope this will help to inform clinicians of the results and improve the treatment of patients. We will send you a lay summary of our findings at the end of the study if you wish. If you would like a copy of the published results please let us know.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that is used in research reports, publications or presentations will refer only to your study ID. Any photographs or videos will be made anonymous by blurring or obscuring your face.

Contact for further information:

If you would like more information please contact Ms. Lisa Tedesco Triccas on 02380 592026 or email ltt1g09@soton.ac.uk.

Thank you once again for taking the time to read this information.

B.1.5 Participant reply slip

Date: 22.07.11
Ethics Number: 11/SC/0345
Version 1

Participant Reply slip

Combining brain stimulation with robot therapy for the impaired arm in early stroke rehabilitation

I am returning this slip to indicate that I am willing to consider taking part in the above study (please tick). ☐

Name: ____

After reading the information sheet provided please provide your preferred contact details so that we can provide further information about the research study.

Telephone Number: ______________________________________

What is the best time to contact you? ________________________________

Email: _______________________________________

Signature (participant) ______________________________________

Date: ______________________________________

Please return this reply slip in the pre-paid addressed envelope to:

Ms. Lisa Tedesco Triccas
Building 45, Faculty of Health Sciences
Highfield Campus
University of Southampton
Southampton
SO17 1BJ

Thank you for your help. A member of the research team will contact you shortly.

B.1.6 Voice Recording Script

We are researchers from the Faculty of Health Sciences at the University of Southampton and we are interested in finding ways to improve arm and hand function after stroke through the use of technologies.

The aim of this research is to find out whether combining non-invasive brain stimulation and robot therapy leads to better recovery than robot therapy alone.

We will now demonstrate what will happen if you take part in this study:

1) At the laboratory, after you have given your consent to take part, the researcher (who is a qualified physiotherapist) will assess you to make sure you are suitable. This will involve asking you questions about your general health and well-being and assessing your affected arm and hand. If you are suitable and you are happy to take part, the research study will then be started.

2) On arrival at the Movement Laboratory you will be met by the researcher. She will show you the equipment and explain the procedures. The researcher will stay with you throughout the whole visit.

3) You will be asked to sit in a normal chair with a back support and your affected arm and hand will be placed in the robot. The robot will support your arm making it feel less heavy. In front of you, there will be a computer screen, which is connected to the robot. By moving your arm, you will be able to play games, shown on the computer.

4) Two sticky pads will be placed on your head. The stimulator will then be switched on. You will not feel anything. Once you are comfortable, you will be asked to play the games for about an hour, with breaks when you want them, about every ten or twenty minutes. The stimulator will only stay on for the first 20 minutes.

5) After an hour the pads will be taken off and you will get out of the robot.

6) You will be invited to attend another 18 visits during the following 8 weeks. Each visit will last for just over an hour. The last will just be an

assessment so we can test whether you have improved and by how much. You will also be asked to come for one more assessment session three months after the treatment has ended.

7) This study involves two groups. One group will receive ‘real’ brain stimulation and robot therapy while the other group will receive ‘placebo’ or ‘sham’ stimulation. This will enable us to test whether including brain stimulation makes any difference. You will be placed in one of the two groups by random selection.

8) Assessments will be done on your first visit, at the end of your 18th and three months following your last visit. The assessments will involve measurements of movements and activities carried out by your affected arm.

9) We will also test the connections between your brain and your affected arm and hand. This will be done using Transcranial Magnetic Stimulation. A single magnetic pulse is sent from a device that the researcher holds above your head. You will hear a click and your arm will move slightly. We measure the strength of the movement by recording tiny electrical signals from your muscles using small sticky pads placed on your skin. The relationship between the strength of the click and the strength of the muscle movement tells us how good the connections are between your brain and your arm and hand.

What are the side effects of taking part?

Non-invasive brain stimulation is painless but in some cases people have said they feel a tingling or itching sensation under the patches when the stimulator is first turned on. Some people have also noticed slight temporary redness under the patches when they are removed. Very rarely, people have reported a slight headache, light flashes in front of the eyes when the stimulator was turned on or off, sleepiness, mood changes, drowsiness, concentration problems and burning of the skin. As a result Transcranial Magnetic Stimulation, there have been very rare reports of people experiencing an epileptic seizure. The risk of any of these side-effects is minimised by our adherence to the recommended safety guidelines. We will monitor you closely throughout the visit and ask you to report any discomfort you had which might be related to the study.

If at any point you feel unwell you may rest for a while or discontinue the session. If you want to withdraw from the study you can do so at any time. You do not have to give a reason and it will not affect your normal care.

Throughout the whole treatment and assessment, someone will be close to you and you can bring along a friend or family member. Refreshments will be provided and travel expenses will be reimbursed. You will be asked to wear loose fitting, comfortable clothing.

If you return the attached form saying you are interested in taking part then you will be contacted by telephone by one of our researchers. They will make an appointment to meet you. Family members or a friend are welcome to be present at the meeting, which can either be on the hospital ward or at your home. You will also have time to think about whether you want to take part and discuss it further with other people such as your healthcare professional or your doctor. If you decide to take part an appointment will be made to come to the Movement Laboratory at the University.

Thank you for watching this video.

B.1.7 Adverts


UNIVERSITY OF Southampton
Have you had a stroke?
Do you have trouble moving your arm?
We are looking for people who have had a stroke to participate in research involving non-invasive brain stimulation and intensive robot therapy for the arm and hand.
To find out more, please contact:
Lisa on 023 8059 2026 | l.tedesco-triccas@soton.ac.uk
Ethics # 11/SC/0345


UNIVERSITY OF Southampton
Have you had a stroke?
Do you have trouble moving your arm?
We are looking for people who have had a stroke to participate in research involving non-invasive brain stimulation and intensive robot therapy for the arm and hand. Data collection will be carried out at Christchurch Hospital.
To find out more, please contact:
Lisa on 023 8059 2026 | l.tedesco-triccas@soton.ac.uk
Ethics # 11/SC/0345

B.2 Information pack-Reliability Study

B.2.1 Participant invitation letter

UNIVERSITY OF Southampton

[28.06.13] [Version number 1]

Dear Sir/Madam,

Re: A study exploring the reliability measurement of brain activity using non-invasive brain stimulation

We would like to invite you to participate in our Physiotherapy research project at the University of Southampton.

We are carrying out a study exploring the accuracy of a type of brain stimulation that is usually used to assess people with neurological conditions. If you are able to and are happy to take part, you will be invited to attend our Movement Laboratory at the University of Southampton on two separate days. The first session will last for 2 hours and the second session will take around an hour.

After giving consent, you will be asked to sit down, wear a cap and sticky pads will be placed on your arm (please refer to the information sheet for more details) while the researcher will take the measurements. We will provide refreshments and regular breaks will be provided.

Attached to this letter is an information sheet that explains in more detail what the study involves. If you have any questions that are not answered in the information sheet you are very welcome to phone us on 02380592026 or e-mail ltt1g09@soton.ac.uk.

If, having read the information sheet, you are interested in taking part in the study; I would be very grateful if you could complete the attached reply slip and return it in the envelope provided.

Thank you

Yours faithfully

Lisa Tedesco Triccas
Research Fellow
Building 45, Faculty of Health Sciences
University of Southampton
Southampton. SO17 1BJ

B.2.2 Participant information sheet- Version 2

[28.06.13] [Version number 2]

Study Title: **A study exploring the reliability measurement of brain activity using non-invasive brain stimulation**

Researcher: Lisa Tedesco Triccas **Ethics number**: 5382

Please read this information carefully before deciding to take part in this research. If you are happy to participate you will be asked to sign a consent form.

What is the research about?

Our names are Lisa Tedesco Triccas, Professor Jane Burridge and Dr Ann-Marie Hughes. We are researchers at the University of Southampton specialising in rehabilitation of people with stroke. We are writing to invite you to take part in a research study that is part of doctoral degree. People with stroke often experience difficulties moving their arm. One new technology that can measure the recovery of arm movement is non-invasive brain stimulation called Transcranial Magnetic Stimulation (TMS). However, in order for this measurement to be accurate, we would like to test it out on healthy adults. This study is sponsored by the University of Southampton and Wessex Medical Research.

What is TMS?

TMS is a non-invasive type of brain stimulation (figure below). This involves placing the blue magnetic figure of eight coil on top of your head and once switched on you will hear a click whereby an electric impulse enters your head.

Why have I been chosen?

This is a convenience sample and you have been chosen because you fit criteria to test the researcher's technique of using the equipment, transcranial magnetic stimulation, on different occasions.

What will happen to me if I take part?

If you return the attached form saying you are interested in taking part you will be contacted by telephone or in person by one of the researchers. This person will discuss the study with you either on the phone or at your home and will answer any questions you might have. If, after this, you would like to take part, an appointment will be made for you to come to the Movement Laboratory at the University. You will be asked to come to the lab for two sessions during one week (separated by three days). The first session will take a maximum of two hours and the second session will take around an hour. Travel expenses will be reimbursed.

At the laboratory, the researcher (who is a qualified physiotherapist) will ask you to give written informed consent to taking part. You will then be assessed to ensure you satisfy the criteria for taking part in the study. This will involve asking you questions about your understanding and assessing your affected arm and hand. If you satisfy the criteria you will be able start on the study straight away.

Each session will involve measuring the nerve connections between your brain and your affected arm and hand. You will be asked to sit in a chair, wear a cap and then glasses. This will be followed by the magnetic coil, Transcranial Magnetic Stimulation, held above your head at a 90 degree angle by the researcher. You will hear a click and then equipment will send a small pulse from your brain to the muscles in your arm and hand. Using electrodes placed on your arm by sticky pads and the computer system, we will be measuring the response in your muscles which will give us information on how good the connections are between your brain and your arm.

Are there any benefits in my taking part?

There is no benefit to taking part but we expect that the results of the study will inform researchers working in the field of stroke rehabilitation, assisting progress towards new strategies for treating the arm and hand.

Are there any risks involved?

TMS is safe procedure used to test the connections from your brain to your arm muscles. When using Transcranial Magnetic Stimulation, there have been reports of people experiencing rare side-effects such as epileptic seizure (less than 1%), and possible side-effects of a headache, neck pain, toothache and hearing changes but this is highly unlikely. We do not anticipate any of these rare side effects as our protocol adheres to the current safety guidelines. We will monitor you closely throughout the visit and ask you to report any discomfort you experience which might be related to the study. If at any point you feel unwell you may rest. If you feel unable to continue you may withdraw. A physiotherapy researcher will be close to you to ensure you are safe at all times.

Will my participation be confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Anonymity will be assured and any information about you that is used in research reports, publications or presentations will refer only to your study ID. We intend to comply with the Data Protection Act/University policy.

What happens if I change my mind?

You have the right to withdraw from the study at any time.

What if there is a problem or I have a complaint?

If you have a concern or a complaint about this study you should contact and discuss the matter with Martina Prude, Head of the Research Governance Office, in the first instance. The address is: University of Southampton, Building 37, Highfield, Southampton, SO17 1BJ **Tel:** +44 (0)23 8059 5058, **Fax:** +44 (0)23 8059 5781, **Email:** rgoinfo@soton.ac.uk. If you remain unhappy you may wish to file a formal complaint about the research conduct and can write a letter to the Associate Dean, Research (Faculty of Health Sciences, Building 67, University of Southampton, Highfield, Southampton SO17 1BJ). The letter should specify the title of the research project and the nature of the complaint.

Where can I get more information?

If you would like more information please contact Ms. Lisa Tedesco Triccas on 02380 592026 or email ltt1g09@soton.ac.uk. Thank you once again for taking the time to read this information.

B.2.3 Participant information sheet- Version 3

[06.12.13] [Version number 3]

Study Title: **A study exploring the reliability measurement of brain activity using non-invasive brain stimulation**

Researcher: Lisa Tedesco Triccas **Ethics number**: 5382

Please read this information carefully before deciding to take part in this research. If you are happy to participate you will be asked to sign a consent form.

What is the research about?

Our names are Lisa Tedesco Triccas, Professor Jane Burridge and Dr Ann-Marie Hughes. We are researchers at the University of Southampton specialising in rehabilitation of people with stroke. We are writing to invite you to take part in a research study that is part of doctoral degree. People with stroke often experience difficulties moving their arm. One new technology that can measure the recovery of arm movement is non-invasive brain stimulation called Transcranial Magnetic Stimulation (TMS). However, in order for this measurement to be accurate, we would like to test it out on healthy adults. This study is sponsored by the University of Southampton and Wessex Medical Research.

What is TMS?

TMS is a non-invasive type of brain stimulation (figure below). This involves placing the blue magnetic figure of eight coil on top of your head and once switched on you will hear a click whereby an electric impulse enters your head.

Why have I been chosen?

This is a convenience sample and you have been chosen because you fit criteria to test the researcher’s technique of using the equipment, transcranial magnetic stimulation, on different occasions.

What will happen to me if I take part?

If you return the attached form saying you are interested in taking part you will be contacted by telephone or in person by one of the researchers. This person will discuss the study with you either on the phone or at your home and will answer any questions you might have. If, after this, you would like to take part, an appointment will be made for you to come to the Movement Laboratory at the University. You will be asked to come to the lab for two sessions during one week (separated by three days). The first session will take a maximum of two hours and the second session will take around an hour. Travel expenses will be reimbursed.

At the laboratory, the researcher (who is a qualified physiotherapist) will ask you to give written informed consent to taking part. You will then be assessed to ensure you satisfy the criteria for taking part in the study. This will involve asking you questions about your understanding and assessing your affected arm and hand. If you satisfy the criteria you will be able start on the study straight away.

Each session will involve measuring the nerve connections between your brain and your affected arm and hand. You will be asked to sit in a chair, wear a cap and then glasses. This will be followed by the magnetic coil, Transcranial Magnetic Stimulation, **held above the right or the left side of your head at a 90 degree angle by the researcher.** You will hear a click and then equipment will send a small pulse from your brain to the muscles in your arm and hand. Using electrodes placed on your arm by sticky pads and the computer system, we will be measuring the response in your muscles which will give us information on how good the connections are between your brain and your arm.

Are there any benefits in my taking part?

There is no benefit to taking part but we expect that the results of the study will inform researchers working in the field of stroke rehabilitation, assisting progress towards new strategies for treating the arm and hand.

Are there any risks involved?

TMS is safe procedure used to test the connections from your brain to your arm muscles. When using Transcranial Magnetic Stimulation, there have been reports of people experiencing rare side-effects such as epileptic seizure (less than 1%), and possible side-effects of a headache, neck pain, toothache and hearing changes but this is highly unlikely. We do not anticipate any of these rare side effects as our protocol adheres to the current safety guidelines. We will monitor you closely throughout the visit and ask you to report any discomfort you experience which might be related to the study. If at any point you feel unwell you may rest. If you feel unable to continue you may withdraw. A physiotherapy researcher will be close to you to ensure you are safe at all times.

Will my participation be confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Anonymity will be assured and any information about you that is used in research reports, publications or presentations will refer only to your study ID. We intend to comply with the Data Protection Act/University policy.

What happens if I change my mind?

You have the right to withdraw from the study at any time.

What if there is a problem or I have a complaint?

If you have a concern or a complaint about this study you should contact and discuss the matter with Martina Prude, Head of the Research Governance Office, in the first instance. The address is: University of Southampton, Building 37, Highfield, Southampton, SO17 1BJ **Tel:** +44 (0)23 8059 5058, **Fax:** +44 (0)23 8059 5781, **Email:** rgoinfo@soton.ac.uk. If you remain unhappy you may wish to file a formal complaint about the research conduct and can write a letter to the Associate Dean, Research (Faculty of Health Sciences, Building 67, University of Southampton, Highfield, Southampton SO17 1BJ). The letter should specify the title of the research project and the nature of the complaint.

Where can I get more information?

If you would like more information please contact Ms. Lisa Tedesco Triccas on 02380 592026 or email ltt1g09@soton.ac.uk. Thank you once again for taking the time to read this information.

B.2.4 Reply slip

UNIVERSITY OF Southampton

Participant Reply slip

A study exploring the reliability measurement of brain activity using non-invasive brain stimulation

I am returning this slip to indicate that I am willing to consider taking part in the above study (please tick). ☐

Name: ______________________________

After reading the information sheet provided please provide your preferred contact details so that we can provide further information about the research study.

Telephone Number: ______________________________

What is the best time to contact you?
____

Email: ______________________________

Signature (participant)______________________________

Date: ______________________________

Please return this reply slip in the pre-paid addressed envelope to:

Ms. Lisa Tedesco Triccas
Building 45, Faculty of Health Sciences
Highfield Campus
University of Southampton
Southampton
SO17 1BJ

Thank you for your help. A member of the research team will contact you shortly.

B.2.5 Advert

[28.06.13] [Version number 1]

A study exploring the reliability measurement of brain activity using non-invasive brain stimulation

A team of researchers from the Faculty of Health Sciences at the University of Southampton are interested in finding ways to improve arm and hand function after stroke through the use of technologies.
The aim of this research is to find out the accuracy of a measurement using brain stimulation that is usually used in the treatment for people with neurological conditions.

If you are a <u>healthy adult</u> (between 40 and 80 years old) and you would like to take part in this research please contact: **Lisa Tedesco Triccas**

Faculty of Health Sciences
Building 45
University of Southampton
Southampton. SO17 1BJ
Tel No: 2380592026
Email: ltt1g09@soton.ac.uk

Appendix C

Ethical and Research and Development Approvals

C.1 Research Ethics Committee Approval Letters

NHS
National Research Ethics Service
NRES Committee South Central - Southampton B
Level 3 Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 3421384
Facsimile: 0117 3420445

27 September 2011

Prof Jane Burridge
Professor of Restorative Neuroscience
University of Southampton
Faculty of Health Sciences
Building 45, Highfield Campus
Southampton
SO17 1BJ

Dear Prof Burridge

Study title: **Combining transcranial direct current stimulation (tDCS) with robot therapy for the impaired upper limb in early stroke rehabilitation.**
REC reference: **11/SC/0345**

Thank you for your letter responding to the Committee's request for further information on the above research.

The further information has been considered on behalf of the Committee by the Vice-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.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Video Script		
Advertisement	1	22 July 2011
Evidence of insurance or indemnity		
GP/Consultant Information Sheets	1	22 July 2011
Investigator CV		
Letter from Sponsor		26 July 2011
Letter of invitation to participant	1	22 July 2011
Other: CV - Student LisaTedesco Triccas		
Other: Reply Slip	1	22 July 2011
Participant Consent Form	1	30 June 2010
Participant Consent Form: Video Consent Form	1	30 June 2010
Participant Information Sheet	2	14 September 2011
Protocol	2	19 September 2011
Questionnaire: Screening	1	14 September 2011
REC application	1	27 July 2011
Referees or other scientific critique report		25 May 2011
Response to Request for Further Information		
Consent Form	1	22 July 2011
Consent Form - Video	1	22 July 2011

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

Reporting requirements

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
- Notification of serious breaches of the protocol
- 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.

Feedback

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.

Further information is available at National Research Ethics Service website > After Review

11/SC/0345	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Dr Helen McCarthy
Chair

Email: scsha.swhrecb@nhs.net

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: *Miss Lisa Tedesco Triccas, University of Southampton*
Mr Danny Pratt

NHS
Health Research Authority

NRES Committee South Central - Southampton B
Bristol REC Centre
Level 3 Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Tel: 0117 3421383
Fax: 0117 3420445

14 June 2012

Professor Jane Burridge
Professor of Restorative Neuroscience
Faculty of Health Sciences
Building 45, University of Southampton
Southampton
SO17 1BJ

Dear Professor Burridge

Study title:	**Combining transcranial direct current stimulation (tDCS) with robot therapy for the impaired upper limb in early stroke rehabilitation.**
REC reference:	**11/SC/0345**
Protocol number:	**N/A**
Amendment number:	**3.2**
Amendment date:	**29 May 2012**

Thank you for submitting the above amendment, which was received on 08 June 2012. I can confirm that this is a valid notice of a substantial amendment and will be reviewed by the Sub-Committee of the REC at its next meeting.

Documents received

The documents to be reviewed are as follows:

Document	Version	Date
Advert	1	08 May 2012
Protocol	3	08 May 2012
Notice of Substantial Amendment (non-CTIMPs)	3.2	29 May 2012
Covering Letter		30 May 2012
Interview Schedules/Topic Guides	1	23 May 2012
Participant Information Sheet	3	23 May 2012
Confirmation email from sponsor		08 June 2012

Notification of the Committee's decision

The Committee will issue an ethical opinion on the amendment within a maximum of 35 days from the date of receipt.

NHS
Health Research Authority

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval for the research.

11/SC/0345:	Please quote this number on all correspondence

Yours sincerely

Barbara Shannon
Assistant Committee Co-ordinator

E-mail: scsha.SWHRECB@nhs.net

Copy to: *Mr Daniel Pratt, Southampton University Hospitals NHS Trust*
Miss Lisa Tedesco Triccas, University of Southampton

C.2 Amendment Letters

NRES Committee South Central - Southampton B
Bristol REC Centre
Level 3 Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT
Tel: 01173 421384
Fax: 01173 420445

05 July 2012

Professor Jane Burridge
Professor of Restorative Neuroscience
Faculty of Health Sciences
Building 45, University of Southampton
Southampton
SO17 1BJ

Dear Professor Burridge

Study title:	**Combining transcranial direct current stimulation (tDCS) with robot therapy for the impaired upper limb in early stroke rehabilitation.**
REC reference:	**11/SC/0345**
Protocol number:	**N/A**
Amendment number:	**3.2**
Amendment date:	**29 May 2012**

The above amendment was reviewed at the meeting of the Sub-Committee held on 27 June 2012.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Advert	1	08 May 2012
Protocol	3	08 May 2012
Notice of Substantial Amendment (non-CTIMPs)	3.2	29 May 2012
Covering Letter		30 May 2012
Participant Information Sheet	3	23 May 2012
Confirmation email from sponsor		08 June 2012
Questionnaire: Hospital Anxiety and Depression Scale		
Interview Schedules/Topic Guides	2	03 July 2012
Consent form for interview	1	23 May 2012

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

11/SC/0346:	Please quote this number on all correspondence

Yours sincerely

Professor Ron King
Chair

E-mail: scsha.swhrecb@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mr Daniel Pratt, Southampton University Hospitals NHS Trust*
Miss Lisa Tedesco Triccas, University of Southampton

NRES Committee South Central - Southampton B

Attendance at Sub-Committee of the REC meeting on 27 June 2012

Name	*Profession*	*Capacity*
Professor Ron King	Mathematician (Retired)	Lay
Dr Kari Nunkoosing	Principal Psychology Lecturer	Lay

Also in attendance:

Name	*Position (or reason for attending)*
Miss Libby Watson	Committee Co-ordinator

NHS

Health Research Authority

NRES Committee South Central - Southampton B

Bristol REC Centre
Level 3 Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT
Tel: 0117 342 1384
Fax: 0117 342 0445

06 March 2013

Miss Lisa Tedesco Triccas
Research Fellow/PhD Student
University of Southampton
Bu.45, Faculty of Health Sciences
University of Southampton
Southampton
SO17 1BJ

Dear Miss Tedesco Triccas

Study title:	**Combining transcranial direct current stimulation (tDCS) with robot therapy for the impaired upper limb in early stroke rehabilitation.**
REC reference:	**11/SC/0345**
Protocol number:	**N/A**
Amendment number:	**Amendment 2, Protocol Version 4**
Amendment date:	**17 January 2013**
IRAS project ID:	**61455**

The above amendment was reviewed at the meeting of the Sub-Committee held on 27 February 2013.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Letter of permission from hospital site	1	25 January 2013
Participant Information Sheet	4	17 January 2013
Protocol	4	17 January 2013
Notice of Substantial Amendment (non-CTIMPs)	Amendment 2, Protocol Version 4	17 January 2013

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

A Research Ethics Committee established by the Health Research Authority

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

11/SC/0346:	**Please quote this number on all correspondence**

Yours sincerely

Dr Giles Tan
Alternate Vice-Chair

E-mail: nrescommittee.southcentral-southamptonb@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mr Daniel Pratt, Southampton University Hospitals NHS Trust*
Professor Jane Burridge, Faculty of Health Sciences
Martina Prude

NRES Committee South Central - Southampton B

Attendance at Sub-Committee of the REC meeting on 27 February 2013

Name	*Profession*	*Capacity*
Mrs Janet Brember	Pharmacist	Expert
Dr Giles Tan - Chair	Consultant Psychiatrist	Expert

Also in attendance:

Name	*Position (or reason for attending)*
Miss Libby Watson	Committee Co-ordinator

C.3 Insurance Letter

UNIVERSITY OF Southampton

Dr Jane Burridge
School of Health Sciences
University of Southampton
University Road
Highfield
Southampton
SO17 1BJ

RGO REF - 8223

18 October 2011

Dear Dr Burridge

Professional Indemnity and Clinical Trials Insurance

Project Title **Combining Transcranial Direct current Stimulation (tDCS) with Robot Therapy for the Impaired Upper Limb in Early Stroke Rehabilitation**

Participant Type:	No Of Participants:	Participant Age Group:	Notes:
Patients	90	Adults	

We have now received notification of NRES approval; we can confirm that insurance is now activated and you may now begin your project.

Good luck with your project.

Yours sincerely

Mrs Ruth McFadyen
Insurance Services Manager

Tel: 023 8059 2417
email: hrm@soton.ac.uk

cc File

Finance Department, University of Southampton, Highfield Campus, Southampton SO17 1BJ United Kingdom
Tel: +44 (0) 23 8059 5000 Fax: +44 (0) 23 8059 2195 www.southampton.ac.uk

C.4 R&D Approval- Southampton

University Hospital Southampton NHS Foundation Trust NHS

Please reply to: Research and Development
SGH - Level E, Laboratory & Pathology
Block, SCBR - MP 138
Southampton General Hospital

Telephone: 02380 794901
Fax: 02380 798678
E-mail: danny.pratt@uhs.nhs.uk

Dr Nicolas Weir
Directorate of Specialist Services
Southampton General Hospital
Tremona Road
Southampton
SO16 6YD

11 July 2012

Dear Dr Weir

ID: RHM NEU0177 Combining transcranial direct current stimulation (tDCS) with robot therapy for the impaired upper limb in early stoke rehabilitation

Thank you for sending us a copy of amendment 3.2 dated 29 May 2012, which has been assessed by R&D. We are pleased to inform you that this amendment does not affect local management approval of your research. We have therefore updated our database and your project file.

Please forward all future amendment applications and approvals to us.

Yours sincerely

Danny Pratt
Research Governance Officer

Solent NHS
NHS Trust
HIOW Shared RM&G Service
2nd Floor Adelaide Health Centre
Western Community Hospital Campus
William Macleod Way
Southampton
Hampshire, SO16 4XE
T: 023 8060 8925
E: sharedrmandg@scpct.nhs.uk

Ref: AB

28th February 2012

Prof. Jane Burridge,
University of Southampton,
Building 45, Faculty of Health Sciences,
Highfield Campus,
University of Southampton.
SO17 1BJ.

Dear Professor Burridge,

RM&G Reference Number: SSPC/090/11
Study title: Combining transcranial direct current stimulation (tDCS) with robot therapy for the impaired upper limb in early stroke rehabilitation

In accordance with the Department of Health's Research Governance Framework for Health and Social Care, all research projects taking place within the Trust must receive a favourable opinion from an ethics committee and permission from the Department of Research and Development (R&D) prior to commencement.

On behalf of Solent NHS Trust, the Shared RM&G Service reviewed the documentation submitted for the above research study and I am pleased to confirm NHS permission. The PICs where you are permitted to undertake the research are listed in the attached appendix. The addition of a new site(s) **must be notified** to the Shared RM&G Service by submitting an SSI form and for PICs, a revised R&D Form.

I would like to bring your attention to the attached list of conditions of approval and specifically to the mandatory requirement to record the recruitment for all sites within this Trust onto the e-dge™ database. Your study will be subject to monitoring and you will be required to comply with the requests in addition to the submission of annual reports.

Documents Reviewed

Document	Version	Date
GP/ Consultant information Sheets	1	22/07/2011
Letter of invitation to participant	1	22/07/2011
Reply slip	1	22/07/2011
Consent form	1	30/06/2010
Video consent form	1	30/06/2010
Participant information sheet	2	14/09/2011
Protocol	2	19/09/2011
R&D form		

I wish you every success with your study and look forward to hearing from you.

Yours sincerely

Alexandra Babbage
Research Governance Officer
Hampshire & IOW Shared RM&G Service

Please send ALL correspondence to:

HIOW Shared RM&G Service
2nd Floor, The Adelaide Health Centre
William Macleod Way
Southampton
Hampshire, SO16 4XE

Tel: 023 8060 8925
Email: Sharedrmandg@scpct.nhs.uk

C.5 R&D- Lymington

Southern Health NHS
NHS Foundation Trust

20 December 2011

Research and Development Department
Academic Centre
College Keep
4-12 Terminus Terrace
SOUTHAMPTON
SO14 3DT

Tel: 023 8071 8540
Fax: 023 8071 8544

www.southernhealthft.nhs.uk

Professor Jane Burridge
Professor of Restorative Neuroscience
Building 45, University of Southampton
Highfield
SOUTHAMPTON
S017 1BJ

Dear Jane

Study Title	**Combining transcranial direct current stimulation (tDCS) with robot therapy for the impaired upper limb in early stroke rehabilitation**		
REC Reference	**11/SC/0345**	**Trust Project N°**	**SHT023**
Protocol N°	**Version 2, 19 September 2011**		
Date of Trust Permission signatory	**20 December 2011**		

Thank you for documentation relating to the above study.

Southern Health Foundation Trust is responsible for Stroke Unit, Lymington Hospital acting as a Participant Identification Centre (PIC) and, in accordance with IRAS guidance, formal research management and governance approval is not required. We note that Dr Durward and his team may identify and refer NHS patients as potential participants.

As members of the research team are employed by University of Southampton they require an Honorary Research Contract or Letter of Access before they start data collection.

Southern Health NHS Foundation Trust has reviewed the request to refer patients, including any resource implications or data protection issues and this letter confirms their permission for Stroke Unit, Lymington Hospital to act as a PIC and proceed with the identification and referral of potential participants.

Yours sincerely

Research & Development

An NHS Teaching Trust with the University of Southampton
Trust Headquarters, Maples, Horseshoe Drive, Tatchbury Mount, Calmore, Southampton SO40 2RZ

C.6 R&D- Bournemouth and Christchurch

The Royal Bournemouth and NHS
Christchurch Hospitals
NHS Foundation Trust

The Royal Bournemouth Hospital
Castle Lane East
Bournemouth
Dorset
United Kingdom
BH7 7DW

Tel: 01202 303626
www.rbch.nhs.uk

Professor Joseph Kwan
Consultant Physician
Stroke Unit
Royal Bournemouth Hospital
Castle Lane East
Bournemouth
BH7 7DW

04/01/2012

Dear Professor Kwan,

Reference: **Combining transcranial direct current stimulation (tDCS) with robot therapy for the impaired upper limb in early stroke rehabilitation.**
REC reference: **11/SC/0345**
UKCRN ID:

I am pleased to inform you that this project has now received approvals from all parties and that you now have formal permission to start.

Please see the Terms and Conditions for undertaking research at the Trust at: http://dorsetresearch.org/docs/drc/TC_for_research_within_DRC.pdf.

Please let me know when you officially start and I would be grateful for a progress report annually.

Good luck with the study,

Dr. R. M. Chapman
Head of Research

Carbon Copy: (CI) Prof Jane Burridge, Faculty of Health Sciences, Building 45, Highfield Campus, Southampton, SO17 1BJ

C.7 R&D- Winchester and Basingstoke

Hampshire Hospitals NHS
NHS Foundation Trust

Research & Development Office
Rm 32, The Lyford Unit, F floor
Basingstoke and North Hampshire Hospital
Aldermaston Road
Basingstoke
Hampshire
RG24 9NA

Tel : 01256 312770
Fax: 01256 314557
christine.poile@hhft.nhs.uk

16 April 2012

Lisa Tedesco Triccas
Research Fellow/ PhD Student
Building 45, Faculty of Health Sciences
University of Southampton
Southampton, SO17 1BJ

Dear Lisa Tedesco Triccas,

Title: **Combining transcranial direct current stimulation (Tdcs) with robot therapy for the impaired upper limb in early stroke rehabilitation**

R&D Ref. No: **2012/MED/12** Ethics Ref. No: **11/SC/0345** CLRN ID:

I am pleased to confirm that Hampshire Hospitals NHS Foundation Trust has reviewed the above project and agreed to act as a Participation Identification Centre (PIC) in this research.

PIC's are not required to complete a Site Specific Information Form nor identify a Principal Investigator for our site. The role of HHFT in this study is for clinicians to identify patients and to introduce the study to them. Potential participants will then need to self-volunteer to the research team. All volunteer screening, consenting and study visits will be undertaken at Southampton University Hospitals NHS Trust.

All serious adverse events should be reported in writing to the appropriate Ethics Committee and also copied to R&D within 7 days of becoming aware of the event.

Please note that this Trust approval only applies to the documents listed below. Any changes to the protocol can only be initiated following further approval from the Ethics Committee via a protocol amendment. All correspondence to the Ethics Committee must be copied to R & D in order to maintain the Trust's R & D approval.

This approval covers both Basingstoke and North Hampshire Hospital and Royal Hampshire County Hospital within the Hampshire Hospitals NHS Foundation Trust.

Document Versions at Approval		
Document	**Version**	**Date**
Study protocol	1	22 Aug 2011
Video Consent Form	1	30 Jun 2010
Consent Form	1	30 Jun 2010
Participant Reply Slip	1	22 Jul 2011
Participant Information Sheet	2	14 September 2011

HHFT R&D Joint Trust Approval letter January 2012 v2
Hospital switchboard 01256 473202
http://www.hampshirehospitals.nhs.uk/

Page 1 of 2
Chairman: Elizabeth Padmore
Chief Executive: Mary Edwards

Hampshire Hospitals NHS
NHS Foundation Trust

Participant Invitation Letter	1	27 Jul 2011
GP Letter	1	22 Jul 2011
SUHT SSI Form	61455/307404/6 /138/153473/239340	

Please contact Ruth Pink or Becci Petch, Research Facilitators, if you require further information.

On behalf of the Trust I wish you every success with the study.

Yours sincerely,

Dr J K Ramage
R&D Director

References

Research governance framework for health and social care 2nd edition 2005
www.dh.gov.uk/assetRoot/04/12/24/27/04122427.pdf

For Clinical Trial Regulations:-
Medicines & Healthcare products Regulatory Authority – www.mhra.gov.uk/index.htm

Data Protection Act - www.opsi.gov.uk/Acts/Acts1998/ukpga_19980029_en_1

Freedom of Information Act - http://www.opsi.gov.uk/Acts/acts2000/ukpga_20000036_en_1

Mental Capacity Act - www.opsi.gov.uk/acts/acts2005/ukpga_20050009_en_1

Human Tissue Act:- www.hta.gov.uk/

For other useful research information :-

Clinical Trials Tool Kit www.ct-toolkit.ac.uk/

MRC Data and Tissues Tool Kit www.dt-toolkit.ac.uk/

C.8 R&D - Chichester

NHS

Sussex NHS Research Consortium

Research Consortium Office
Worthing Hospital
Lyndhurst Road
Worthing
West Sussex
BN11 2DH

Tel: 01903 285027
Fax: 01903 209884
www.sxrc.nhs.uk

Miss Lisa Tedesco-Triccas
Doctoral Student
University of Southampton
Building 45,
Faculty of Health Sciences
Highfield Campus
Southampton
SO17 1BJ

07/03/2013

Dear Miss Tedesco-Triccas,

Our ID: 1532/NOCI/2013
TITLE: Combining transcranial direct current stimulation (tDCS) with robot therapy for the impaired upper limb in early stroke rehabilitation.

Thank you for your submission of the above project through NIHR CSP to access Participant Identification Centres (PICs) in our area.

All the mandatory CSP governance checks have been satisfied, and I am therefore pleased to confirm that you now have our agreement for the following sites to act as PICs:

- **Western Sussex Hospitals NHS Trust – Dr Lloyd Bradley, St. Richard's Hospital, Chichester.**

Please note that the above PIC sites do not indemnify the main research site, the organisation managing the research or the participants in relation to the conduct or management of the research – this responsibility rests with the study sponsor.

Your research governance approval is valid providing you comply with the conditions set out below:

1. You commence your research within one year of the date of this letter. If you do not begin your work within this time, you will be required to resubmit your application.
2. You notify the Consortium Office should you deviate or make changes to the approved documents.
3. You alert the Consortium Office by contacting me, if significant developments occur as the study progresses, whether in relation to the safety of individuals or to scientific direction.
4. You complete and return the standard annual self-report study monitoring form when requested to do so at the end of each financial year. Failure to do this will result in the suspension of research governance approval.
5. You comply fully with the Department of Health Research Governance Framework, and in particular that you ensure that you are aware of and fully discharge your responsibilities in respect to Data Protection, Health and Safety, financial probity, ethics and scientific quality. You should refer in particular to Sections 3.5 and 3.6 of the Research Governance Framework.

ZONE

6. You ensure that all information regarding patients or staff remains secure and strictly confidential at all times. You ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice, Data Protection Act and Human Rights Act. Unauthorised disclosure of information is an offence and such disclosures may lead to prosecution.

Good luck with your work.

Yours sincerely,

Miss Hannah Haines
Senior Research Governance Officer

Email: Hannah.haines@wsht.nhs.uk
Tel: 01903 285222 Ext 4394
Fax: 01903 209884

cc.: Dr Lloyd Bradley, Consultant in Rehabilitation Medicine, Western Sussex Hospitals NHS Trust.
Mrs Clare Meachin, Lead Research Studies Manager, Western Sussex Hospitals NHS Trust.

C.9 Reliability Study Ethical approval

Submission Number 5382:

Submission Title A study exploring the reliability measurement of brain activity using non-invasive brain stimulation:

The Research Governance Office has reviewed and approved your submission

You can begin your research unless you are still awaiting specific Health and Safety approval (e.g. for a Genetic or Biological Materials Risk Assessment) or external ethics review (e.g. NRES).If your study is classified as requiring NRES review and you are being sponsored by the University of Southampton you will receive a paper notification of sponsorship from the Research Governance Office which will enable you to submit for NRES review.

If you do not receive this within two working weeks or have any queries please email rgoinfo@soton.ac.uk quoting your ERGO submission ID number.The following comments have been made:

This is to confirm the University of Southampton is prepared to act as 'Research Sponsor' for this study, and the work detailed in the protocol/study outline will be covered by the University of Southampton insurance programme.

As the Sponsor's representative for the University this office is tasked with:

1. Ensuring the researcher has obtained the necessary approvals for the study

2. Monitoring the conduct of the study

3. Registering and resolving any complaints arising from the study

As the Chief/Principle Investigator you are responsible for the conduct of the study and you are expected to:

1. Ensure the study is conducted as described in the protocol/study outline approved by this office

2. Advise this office of any change to the protocol, methodology, study documents, research team, participant numbers or start/end date of the study

3. Report to this office as soon as possible any concern, complaint or adverse event arising from the study

Failure to do any of the above may invalidate your ethics approval and therefore the insurance agreement, affect funding and/or sponsorship of your study; your study may need to be suspended and disciplinary proceedings may ensue.

On receipt of this letter you may commence your research but please be aware other approvals may be required by the host organisation if your research takes place outside the University. It is your responsibility to check with the host organisation and obtain the appropriate approvals before recruitment is underway in that location.

May I take this opportunity to wish you every success for your research

Submission ID : 5382

Submission Name: A study exploring the reliability measurement of brain activity using non-invasive brain stimulation

Date : 11 Jul 2013

Created by : Lisa Tedesco Triccas

ERGO : Ethics and Research Governance Online

http://www.ergo.soton.ac.uk

DO NOT REPLY TO THIS EMAIL

Appendix D

Consent Forms and letters

D.1 Randomised controlled trial consent form

Date: 30.06.10

Ethics Number: 11/SC/0345

Version 1

Title of Project: Combining brain stimulation with robot therapy for the impaired arm in early stroke rehabilitation

Name of Researcher: Lisa Tedesco Triccas

Tel: 023 8059 2026

Name of Principal Investigator: Professor Jane Burridge

Tel: (0)23 8059 8885

Faculty of Health Sciences, University of Southampton

Please initial box

1. I confirm that I have read and understand the information sheet Dated______________, Version 2 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. Should you lose capacity to consent during the study, data already collected with consent will be retained and used in the study. ☐

3. I understand that if the sensation of the stimulation is uncomfortable I would be able to withdraw from the study at any time. ☐

4. (Optional) I give permission to the researcher to inform my GP of my participation in this study. ☐

5. I understand that at the end of the study data collected from me will be securely stored at the University of Southampton for 10 years. ☐

6. (Optional) I would like to receive a brief summary describing the study's results when it is completed. ☐

7. I agree to place my name in the Participant Research Register of the Faculty of Health Sciences in order to be included in other related research. ☐

8. I agree to take part in the above study. ☐

____

Name of Participant

____

Signature

____

Date

____

Researcher

____

Signature

____

Date

____

D.2 Randomised controlled trial video consent form

Title of Project: Combining brain stimulation with robot therapy for the impaired arm in early stroke rehabilitation

Name of Researcher: Lisa Tedesco Triccas
Tel: 023 8059 5297
Name of Principal Investigator: Professor Jane Burridge,
Tel: (0)23 8059 8885
Faculty of Health Sciences, University of Southampton

Please initial box

1. I agree to being filmed or photographed while performing movement tests or treatment programme and for video footage to be viewed by a researcher for analysis. ☐

2. I understand that by withholding my consent to having my photograph or video taken will not exclude me from the study ☐

______________________________ ____________________________

Name of Participant Signature

____

Date

______________________________ ____________________________

Researcher Signature

____

Date

D.3 Interview consent form

Date: 23.05.10

Ethics Number: 11/SC/0345

Version 1

Title of Project: Combining brain stimulation with robot therapy for the impaired arm in early stroke rehabilitation

Name of Researcher: Lisa Tedesco Triccas Tel: (0) 23 8059 2026

Name of Principal Investigator: Professor Jane Burridge

Tel: (0)23 8059 8885

Faculty of Health Sciences, University of Southampton

Please initial box

1 I confirm that I have read and understand the information sheet dated .... for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2 I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my legal rights being affected. ☐

3 I understand that the meeting will be audio recorded and transcribed ☐

4 I understand that, although no names or identifying comments will be included, direct quotes may be used in the write up of the study. ☐

5 I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Researcher	Date	Signature

D.4 Letter to the GP

Dr………………………………………………….

Date

Re: Patient participation in University of Southampton Clinical Research Study

Study Title: 'Combining transcranial direct current stimulation (tDCS) with robot therapy for the impaired upper limb in early stroke rehabilitation'

Dear Dr………………………..

I am writing to you to inform you that *Participant Name* has consented to participate in a clinical trial investigating the combination of non-invasive brain stimulation and robot therapy for the impaired upper limb at the Faculty of Health Sciences, University of Southampton. *Participant Name* has given permission for me to inform you about their decision to participate in the study which is scheduled to commence on the (*Provide date*) and run until (*Provide date)*.

Full ethical approval from the IRAS Ethics Committee (11/SC/0345) has been granted for the above study and the study is sponsored and insured by the University of Southampton. Please do not hesitate to contact me should you need further information. Please contact me at your earliest convenience should you have any concerns about *Participant Name* participating in this University of Southampton study.

Please find enclosed a copy of the study participant information sheet for your own reference.

Yours sincerely,

Lisa Tedesco Triccas
Research Fellow
Building 45
Faculty of Health Sciences
University of Southampton
SO17 1BJ
Tel. No: +44 (0) 2380595297
Email: ltt1g09@soton.ac.uk

D.5 Reliability consent form

[28.06.13] [Version number 1]

Study title: A study exploring the reliability measurement of brain activity using non-invasive brain stimulation

Researchers name: Lisa Tedesco Triccas, Professor Jane Burridge, Dr Ann-Marie Hughes
Study reference: 5369
Ethics reference: 5369

Please initial the boxes if you agree with the statement(s):

I have read and understood the information sheet (06.12.13/version no. 2) of participant information sheet) and	☐
I agree to take part in this research project and agree for my data to be used for the purpose of this study	☐
I understand my participation is voluntary and I may withdraw at any time without my legal rights being affected	☐
I am happy to be contacted regarding other unspecified research projects. I therefore consent to the University retaining my personal details on a database, kept separately from the research data detailed above. The 'validity' of my consent is conditional upon the University complying with the Data Protection Act and I	☐
I understand that if the sensation of the stimulation is uncomfortable I would be able to withdraw from the study at any time.	☐

Data Protection
I understand that information collected about me during my participation in this study will be stored on a password protected computer and that this information will only be used for the purpose of this study. All files containing any personal data will be made anonymous.

Name of participant (print name)……………………………………………………

Signature of participant……………………………………………………………..

Date……………………………………………………………………………………

Appendix E

Screening, Clinical Measures and Reports

E.1 Assessment lab sheet

Date: ___________________

Participant Number: _________________

1. Before participant arrives:	
i) Arrange set up of lab - heater - pillow - wooden chair with arms - non slip mat - spare batteries for data logger 4xAA	
ii) Set up Brain sight - Set up camera - Add MRI if possible - Peel depth at 6-8mm (to see grey white interface rotate to same as patient) - Save participant number - Secure LED balls of glasses - Place chair - Calibrate coil with equipment every visit	
iii) Place laptop to the left or right of participant	
iv) Set up lap top and TMS with Datalog and EMG equipment	

2. Once participant arrives:	
i) Participant is welcomed at the foyer	
ii) Questions answered about the study	
iii) Consent form	

3. *Check Criteria :*	
Participants should have: • A confirmed clinical diagnosis of stroke by a neurologist or stroke specialist • Age 18-80 years • No previous history of another stroke	

• >2weeks post-stroke • Upper and fore-arm and hand paresis (MRC grading > 2) with minimal spasticity allowed (Modified Ashworth scale <or= 2) • Some shoulder flexion • Good sitting balance; sufficient to maintain sitting posture in an armchair • Ability to provide informed consent	
Subjects excluded if they: • Have impaired gross cognitive function; score of less than 24 of the Mini-Mental State Examination (Folstein et al. 1975) • Have any another neurological condition apart from stroke • Have shoulder pain 0-90 degrees • Have a history of epilepsy • Implants within the brain • Previous brain neurosurgery • Have metal implants in the head including cochlear implants • Are taking medications that influence cortical excitability • Previous adverse effects when stimulated with tDCS or Transcranial Magnetic Stimulation (TMS). • Are pregnant	

4. Demographic Data						
Participant	Gender	Age	Handiness	Weeks/Months from stroke	Lesion location	Type of stroke

5. Clinical Measures (blinded assessor)	
• Stroke Impact Scale (SIS)	
• ARAT	
• FMA	
• Motor Activity Log-28	
• Modified Tardieu Scale (MTS)	

6. Brainsight Validation	
Put on cap on the participant (do not cover ear) Place tape strips	

Participant wear glasses LED should face the camera Do not move glasses	
Pointer placed on 5 specific points - Right ear - Left ear - Nasian - Tip of nose - Right eye	
Place pointer on site of hot spot (vertical)	
Press sample now	
Name it	
Choose view 2x1	
Change to coil	

7. *Neurophysiological Measures* *Preparation*	
a) Participant is seated on a comfortable well supported chair	
b) A non-slip mat is placed under feet	
c) Participant cannot cross lower limbs	
d) No talking during measurements	
e) Place electrodes on Extensor digitorum and deltoid muscle	
f) EMG switched on and set up	
g) TMS switched on and set up	
h) TMS button is pushed	
i) Hot spot is found at RMT *Min 50microV in 5/10 consecutive stimulation* *If no response increase intensity to 100% of stim output* *If still no response check next visit.*	
j) Hot spot marked (4cm lat to vertex)	

Muscle	Hot spot Measurement (cm) Lateral/anterior/posterio	RMT
Deltoid		

Extensor Digitorum		

8. Brainsight and Hotspot	
Place pointer on site of hot spot (vertical)	
Press sample now	
Name it	
Choose view 2x1	
Change to coil	

4mm for recruiting hotspot (don't worry about angle)

9. A) Recruitment Curve Measurement	
Deltoid	Amplitude
90% before measurement	
RMT	
110%	
120%	
130%	
140%	
150%	
160%	

10. B) Recruitment Curve Measurement	
Extensor Digitorum	Amplitude
90% before measurement	
RMT	
110%	
120%	
130%	
140%	
150%	
160%	

Measure Active Motor Threshold (AMT) – lower than RMT

	AMT
Deltoid	
ED	

Measure Silent Period

Ask patient to raise shoulder 20% of max volume activity

Active movement at 100microvolt (5% less than RMT)

5 sec between stimuli

Save recordings

E.2 Treatment lab sheet

Contact Margaret regarding type of treatment

1) Intervention	
1) Patient is seated in front of the robot	
2) Robot is adjusted according to height and side of stroke	
3) Robot is set up	
4) Wash electrodes in saline	
5) tDCS electrodes are placed on M1 area and supraorbital region using coban band and gel	

6) Elastic band placed to hold electrodes	
7) Robot is switched on -move robot as much as possible left or right -foot stand under chair -shoulder bar just left or right to shoulder -keep fixed -adjust length by screw side and front -adjust hand one -adjust tension -unlock robot -write settings on Armeo	
8) tDCS is switched on (real/sham)	
9) tDCS switched off after 20 minutes	
10) RT continued for another 40 minutes	

E.3 Screening Assessments

E.3.1 Mini-mental state examination

Sheets were purchased from Par

Mini-Mental State Examination (MMSE)

Patient's Name: ______________________ Date: __________

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

E.3.2 Modified ashworth scale and MRC strength testing

Name	Date

Modified Ashworth Scale

R/L	Muscle under stretch	Score

The modified Ashworth scale

0. No increase in muscle tone
1. Slight increase in tone with a catch and release or minimal resistance at end of range
2. As 2 but with minimal resistance through range following catch
3. More marked increase tone through ROM
4. Considerable increase in tone, passive movement difficult.
5. Affected part rigid

Joint range of motion, active and passive

R/L	Flex/Ex	Joint to be tested	Passive ROM	Active ROM

ROM range of movement

Degrees from extension

Muscle strength

R/L	Muscle	Score

MRC score

0. No movement
1. Palpable contraction, no visible movement
2. Movement but only with gravity eliminated
3. Movement against gravity
4. Movement against resistance but weaker than normal
5. Normal power

E.3.3 TMS questionnaire

Consensus was also reached for the following questionnaire that will be used in the proposed study to screen people before TMS will be applied (Rossi et al. 2011):

1) Do you have epilepsy or have you ever had a convulsion or a seizure?

(2) Have you ever had a fainting spell or syncope? If yes, please describe on which occasion(s)?

(3) Have you ever had a head trauma that was diagnosed as a concussion or was associated with loss of consciousness?

(4) Do you have any hearing problems or ringing in your ears?

(5) Do you have cochlear implants?

(6) Are you pregnant or is there any chance that you might be?

(7) Do you have metal in the brain, skull or elsewhere in your body (e.g., splinters, fragments, clips, etc.)? If so, specify the type of metal.

(8) Do you have an implanted neurostimulator (e.g., DBS, epidural/subdural, VNS)?

(9) Do you have a cardiac pacemaker or intracardiac lines?

(10) Do you have a medication infusion device?

(11) Are you taking any medications? (please list)

(12) Did you ever undergo TMS in the past? If so, were there any problems.

(13) Did you ever undergo MRI in the past? If so, were there any problems.

It should be noted that affirmative answers to questions 1-13 do not represent absolute contraindications to TMS, but the team of researchers will make a decision on the suitability of the participant for receiving single-pulse TMS based on the answers provided. The following two examples hopefully clarify this process:

1. Participant X answers only affirmative to question 4 and states that ‘his wife tells him that his hearing has decreased over the last years.’ We would not see this as a contraindication for the application of TMS in this subject. According to the 2009 Guidelines, all participants will wear ear plugs any way. Furthermore, the position of the TMS coil in our study is relatively far away from the hearing system in our adult participants.

2. Participant Y reports that he sustained seizures after his stroke and that he is treated with anti-epilepsy medication. He also has a cardiac pace-maker. Based on this information, we would not find this participant suitable for TMS administration and exclude him from the study.

E.4 Clinical Assessments

E.4.1 Fugl-meyer assessment

FUGL-MEYER ARM SCORE

Primarily assessed side: left ☐ or right ☐

A. SHOULDER-ELBOW-FOREARM		
I REFLEX-ACTIVITY (patient sitting, verbalise the findings) *Biceps, Triceps, Fingerflexors*	- no reflex-activity ☐ 0 - reflex-activity in biceps and/or fingerflexors ☐ 2 - no reflex-activity ☐ 0 - reflex-activity in extensors ☐ 2	**TOTAL** **/4**
II ACTIVE MOVEMENTS IN SYNERGIES (patient sitting with the back against the backrest) *a) Flexor synergy*: "hand to your (ipsilateral) ear" with shoulder retraction forearm elbow shoulder *b) Extensor synergy:* "knuckles on contralateral knee" from flexor synergy (eventually passive) Ask the patient to place knees apart. Verbalise the findings. forearm elbow shoulder	none / partial / perfect supination: ☐ 0 ☐ 1 ☐ 2 flexion: ☐ 0 ☐ 1 ☐ 2 outw rotation: ☐ 0 ☐ 1 ☐ 2 abduction (90°) ☐ 0 ☐ 1 ☐ 2 elevation: ☐ 0 ☐ 1 ☐ 2 retraction: ☐ 0 ☐ 1 ☐ 2 none / partial / perfect pronation: ☐ 0 ☐ 1 ☐ 2 extension: ☐ 0 ☐ 1 ☐ 2 adduction + int rotation ☐ 0 ☐ 1 ☐ 2	**/18**
III DYN. FLEXOR+EXTENSOR SYNERGY (patient sitting) *a) Hand to lumbar spine* "bring your hand on your back" *b) Shoulder flexion 0° to 90°* elbow extended, forearm in midposition "bring your extended arm up, thumb upwards". The assessor may assist the patient to get into the starting position.	- the specific detail cannot be performed at all ☐ 0 - hand behind ant sup iliac spine but does not reach the spine ☐ 1 - the detail is performed faultlessly ☐ 2 - arm immediately in abduction or elbow in flexion ☐ 0 - cannot cover full range or shoulder abduction and/or elbow in flexion occurs ☐ 1 - the detail is performed faultlessly ☐ 2	

c) Pro-Supination of the forearm elbow flexed 90°, shoulder 0°	- starting position impossible and/or no pro-supination ☐ 0 - limited pro-supination and/or starting position possible and kept during the movement, ☐ 1 - the detail is performed faultlessly ☐ 2	**/6**
IV ACTIVE MOVEMENT, WITH LITTLE OR NO SYNERGY (patient sitting) *a) Shoulder abduction 0° to 90°* elbow fully extended and forearm pronated The assessor may assist the patient to get into the starting position. *b) Shoulder flexion 90° to 180°* arm in adduction, elbow extended and forearm in midposition, "bring extended arm up, thumb up" The assessor may assist the patient to get into the starting position. *c) Pro-Supination of the forearm* shoulder 30° - 90° flexion, elbow in extension Score against the passive RoM, don´t mistake the rotation of the glenohumeral joint.	- immediately supinated and/or elbow flexed ☐ 0 - partly performed or elbow is flexed or fore-arm can not be kept in pronated position ☐ 1 - the detail is performed faultlessly ☐ 2 - arm immediately in abd. or elbow flexed ☐ 0 - arm not immediately in abduction and/or elbow in flexion ☐ 1 - the detail is performed faultlessly ☐ 2 - starting position impossible and/or no pro-sup ☐ 0 - starting position possible and kept during the movement, limited pro-sup ☐ 1 - the detail is performed faultlessly ☐ 2	**/6**
V NORMAL REFLEX-ACTIVITIES Only assessed if in the previous section total score = 6	a) not assessed (because score of A. IV < 6) ☐ 0 b) assessed: - ≥ 2 of 3 reflex-activities are markedly hyperactive ☐ 0 - 1 reflex markedly hyperactive or ≥ 2 lively ☐ 1 - no hyperactive reflexes ☐ 2	**/2**
B. WRIST		
a) Wrist stability in 15° dorsal flexion shoulder 0°, elbow 90°, forearm fully pronated Assessor may bring and keep the elbow in the required position. *b) Max. wrist flexion - extension* shoulder in 0°, elbow 90°, forearm pronated Assessor may support the elbow in the required position. *c) Wrist stability in 15° dorsiflexion* shoulder slightly flexed and/or abducted, elbow extended, forearm pronated Assessor may support the elbow in this position.	- 15° dorsiflexion not achieved ☐ 0 - wrist dorsiflexion performed, no resistance ☐ 1 - position can be maintained against some (slight) resistance ☐ 2 - no active repeated movements ☐ 0 - active movements less than passive range ☐ 1 - detail is fully and adequately performed ☐ 2 - dorsiflexion to required position not possible ☐ 0 - required wrist position possible, no resistance ☐ 1 - required position can be maintained against some (slight) resistance ☐ 2	

d) Max. wrist flexion - extension shoulder slightly flexed and/or abducted, elbow extended, forearm pronated Assessor may support the elbow if needed.	- no active repeated movements ☐ 0 - active movements smaller than passive movements ☐ 1 - detail is fully and adequately performed ☐ 2	
e) Circumduction of the wrist shoulder 0°, elbow 90°. Assessor may provide support for the forearm but not restrain it.	- circumduction cannot be performed ☐ 0 - jerky or incomplete movements ☐ 1 - detail is fully and adequately performed ☐ 2	**/10**
C. HAND (assessor may support the elbow in 90° position; not the wrist)		
a) Flexion of the fingers	- no flexion ☐ 0 - some, but not full active flexion ☐ 1 - full active flexion compared with the unaffected hand ☐ 2	
b) Extension of the fingers from the position of full flexion (passive)	- no extension ☐ 0 - some, but not full ext. or release of an active mass flexion grasp ☐ 1 - full active extension, compared with the unaffected hand ☐ 2	
c) Grasp A: extension MCP, flexion PIP and DIP grasp is tested against resistance	- required position not possible ☐ 0 - grasp is weak ☐ 1 - grasp maintained against relatively great resistance ☐ 2	
d) Grasp B: extended index and thumb patient should perform a pure thumb adduction (holding a scrap of paper against a vertical tug)	- the function can not be performed ☐ 0 - scrap of paper kept in place, not against a slight tug ☐ 1 - scrap of paper is held well against a tug ☐ 2	
e) Grasp C: pulpa thumb against the pulpa of the index (holding a pencil against a horizontal tug)	- the function can not be performed ☐ 0 - pencil kept in place, not against a slight tug ☐ 1 - pencil is held well against a tug ☐ 2	
f) Grasp D: volar surface of the thumb and index against each other (holding a cylinder-shaped object against a horizontal tug)	- the function can not be performed ☐ 0 - cylinder kept in place, not against a slight tug ☐ 1 - cylinder is held well against a tug ☐ 2	
g) Grasp E: spherical grasp (grasping a tennisball and holding it against a tug)	- the function can not be performed ☐ 0 - ball grasped, not held against a slight tug ☐ 1 - ball grasped, well held against a tug ☐ 2	**/14**

D. COORDINATION/ SPEED (no compensation of trunk - head allowed)		

Finger-to-nose test: eyes closed, starting position is abduction, 5 times				
a) T*remor*	marked ☐ 0	slight ☐ 1	no ☐ 2	
b) Dysmetria	pronounced or unsystematic ☐ 0	slight and systematic ☐ 1	no ☐ 2	
c) Time compare time affected to unaffected side	> 6 sec ☐ 0	2-5 sec ☐ 1	< 2 sec ☐ 2	
	time right: sec.	time left: sec.		**/6**
	TOTAL MOTOR FUNCTION, UPPER LIMB			**.../66**

E.4.2 Action research arm test Scoring Sheet

Test Number	Item	Score	
		Left	Right
Grasp subscale			
1	Block, $10cm^3$	0 1 2 3	0 1 2 3
2	Block, $2.5cm^3$	0 1 2 3	0 1 2 3
3	Block, $5cm^3$	0 1 2 3	0 1 2 3
4	Block, $7.5cm^3$	0 1 2 3	0 1 2 3
5	Cricket ball	0 1 2 3	0 1 2 3
6	Sharpening stone	0 1 2 3	0 1 2 3
		Subtotal ______/18	Subtotal ______/18
Grip subscale			
7	Pour water from one glass to another	0 1 2 3	0 1 2 3
8	Displace 2.25-cm alloy tube from one side of table to the other	0 1 2 3	0 1 2 3
9	Displace 1-cm alloy tube from one side of table to the other	0 1 2 3	0 1 2 3
10	Put washer over bolt	0 1 2 3	0 1 2 3
		Subtotal ______/12	Subtotal ______/12
Pinch subscale			
11	Ball bearing, held between ring finger and thumb	0 1 2 3	0 1 2 3
12	Marble, held between index finger and thumb	0 1 2 3	0 1 2 3
13	Ball bearing, held between middle finger and thumb	0 1 2 3	0 1 2 3
14	Ball bearing, held between index finger and thumb	0 1 2 3	0 1 2 3
15	Marble, held between ring finger and thumb	0 1 2 3	0 1 2 3
16	Marble, held between middle finger and thumb	0 1 2 3	0 1 2 3
		Subtotal ______/18	Subtotal ______/18
Gross Movement subscale			
17	Hand to behind the head	0 1 2 3	0 1 2 3
18	Hand to top of head	0 1 2 3	0 1 2 3
19	Hand to mouth	0 1 2 3	0 1 2 3
		Subtotal ____/9	Subtotal ____/9
		Total _____/57	Total ______/57

There are 4 subscales. Te tests in each are ordered so that if subject scores 3 on the first test, no more tests need to be administered in that subscale, and the subject automatically scores top marks (all 3s) for all tests in that subscale. If subject fails the first test (score 0) and fails the second, test (score 0) of the subscale, the subject automatically scores zero for all tests in that subscale, and again no more tests needed to be performed in that subscale; and (3) otherwise the subject needs to complete all tasks within the subtest Score: 3 = subject performed the test normally within 5 seconds; 2 = subject could complete the test but took abnormally long (5 to 60 seconds) or had great difficulty; 1 = subject could only partially perform the test within 60 seconds; and 0 = subject could not perform any part of the test within 60 seconds.

E.4.3 Modified tardieu scale

Quality of muscle reaction (X):

Grade	Description
0	No resistance throughout the course of the passive movement.
1	Slight resistance throughout the course of the passive movement, with no clear catch at a precise angle.
2	Clear catch at a precise angle, interrupting the passive movement, followed by a release.
3	Fatigable clonus (<10 seconds when maintaining pressure) occurring at a precise angle.
4	Infatigable clonus (>>10 seconds when maintaining pressure) occurring at a precise angle.
5	Joint is immoveable.

Angle of Catch at Fast Movement (R1)

Elbow Flexors:

Wrist Flexors:

E.4.4 Motor Activity Log-28

Participant___________________ Date _________ Visit _______

Assessor_________

Motor Activity Log

Amount Scale

1. Turn on a light with affected arm ____ ____ if no, why? (use code)

2. Open drawer ____ ____ if no, why? (use code)

3. Remove an item of clothing from drawer ___ if no, why? (use code)

4. Pick up phone ____ ____ if no, why? (use code)

5. Wipe off a kitchen counter or other surface____ ____ if no, why? (use code)

6. Get out of a car ____ ____ if no, why? (use code)

7. Open refrigerator ____ ____ if no, why? (use code)

8. Open a door by turning a door knob handle ____ ____ if no, why? (use code)

9. Use a TV remote control____ ____ if no, why? (use code)

10. Wash your hands ____ ____ if no, why? (use code)

Codes for recording "no" responses:

1. "I used the unaffected arm entirely." (assign "0").

2. "Someone else did it for me." (assign "0").

3. "I never do that activity, with or without help from someone else because it is impossible." For example, combing hair for people who are bald. (assign "N/A" and drop from list of items).

4. "I sometimes do that activity, but did not have the opportunity since the last time I answered these questions." (carry-over last assigned number for that activity).

5. Non-dominant hand hemiparesis. (only applicable to #24; assign "N/A" and drop from list of items).

11. Turning water on/off with know____ ____ if no, why? (use code)

12. Dry your hands ____ ____ if no, why? (use code)

13. Put on your socks ____ ____ if no, why? (use code)

14. Take off your socks ____ ____ if no, why? (use code)

15. Put on your shoes ____ ____ if no, why? (use code)

16. Take off your shoes ____ ____ if no, why? (use code)

17. Get up from a chair with arm rests ____ ____ if no, why? (use code)

18. Pull chair away from table before sitting down ____ ____ if no, why? (use code)

19. Pull chair toward table after sitting down ____ ____ if no, why? (use code)

20. Pick up a glass, bottle, drinking cup or can____ ____ if no, why? (use code)

21. Brush your teeth ____ ____ if no, why? (use code)

22. Use a key to unlock a door ____ ____ if no, why? (use code)

23. Carry an object in your hand ____ ____ if no, why? (use code)

24. Use a fork or spoon for earting ____ ____ if no, why? (use code)

25. Comb your hair ____ ____ if no, why? (use code)

26. Pick up a cup by a handle ____ ____ if no, why? (use code)

27. Button a shirt ____ ____ if no, why? (use code)

38. Eat half a sandwich or finger food ____ ____ if no, why? (use code)

How Well Scale (HW)

0 - The weaker arm was not used at all for that activity (never).

.5

1 - The weaker arm was moved during that activity but was not helpful (very poor).

1.5

2 - The weaker arm was of some use during that activity but needed some help from the stronger arm or moved very slowly or with difficulty (poor).

2.5

3 - The weaker arm was used for the purpose indicated but movements were slow or were made with only some effort (fair).

3.5

4 - The movements made by the weaker arm were almost normal, but were not quite as fast or accurate as normal (almost normal).

4.5

5 - The ability to use the weaker arm for that activity was as good as before the stroke (normal).

Possible Reasons for Not Using the Weaker Arm for the Activity:

Reason A. “I used the unaffected arm entirely.”

Reason B. “Someone else did it for me.”.

Reason C. “I never do that activity, with or without help

from someone else because it is impossible.” For example,

combing hair for people who are bald.

Reason D. “I sometimes do that activity, but did not have the opportunity since the last time I answered these questions.”

Reason E. "That is an activity that I normally did only with my dominant hand before the stroke, and continue to do with my dominant hand now."

E.4.5 Stroke Impact Scale

Stroke Impact Scale

These questions are about the physical problems which may have occurred as a result of your stroke.

1. In the past week, how would you rate the strength of your....	**A lot of strength**	**Quite a bit of strength**	**Some strength**	**A little strength**	**No strength at all**
a. Arm that was most affected by your stroke?	5	4	3	2	1
b. Grip of your hand that was most affected by your stroke?	5	4	3	2	1
c. Leg that was most affected by your stroke?	5	4	3	2	1
d. Foot/ankle that was most affected by your stroke?	5	4	3	2	1

These questions are about your memory and thinking.

2. In the past week, how difficult was it for you to...	**Not difficult at all**	**A little difficult**	**Somewhat difficult**	**Very difficult**	**Extremely difficult**
a. Remember things that people just told you?	5	4	3	2	1
b. Remember things that happened the day before?	5	4	3	2	1
c. Remember to do things (e.g. keep scheduled appointments or take medication)?	5	4	3	2	1
d. Remember the day of the week?	5	4	3	2	1
e. Concentrate?	5	4	3	2	1
f. Think quickly?	5	4	3	2	1
g. Solve everyday problems?	5	4	3	2	1

These questions are about how you feel, about changes in your mood and about your ability to control your emotions since your stroke.

3. In the past week, how often did you...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Feel sad?	5	4	3	2	1
b. Feel that there is nobody you are close to?	5	4	3	2	1
c. Feel that you are a burden to others?	5	4	3	2	1
d. Feel that you have nothing to look forward to?	5	4	3	2	1
e. Blame yourself for mistakes that you made?	5	4	3	2	1
f. Enjoy things as much as ever?	5	4	3	2	1
g. Feel quite nervous?	5	4	3	2	1
h. Feel that life is worth living?	5	4	3	2	1
i. Smile and laugh at least once a day?	5	4	3	2	1

The following questions are about your ability to communicate with other people, as well as your ability to understand what you read and what you hear in a conversation.

4. In the past week, how difficult was it to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Extremely difficult
a. Say the name of someone who was in front of you?	5	4	3	2	1
b. Understand what was being said to you in a conversation?	5	4	3	2	1
c. Reply to questions?	5	4	3	2	1
d. Correctly name objects?	5	4	3	2	1
e. Participate in a conversation with a group of people?	5	4	3	2	1
f. Have a conversation on the telephone?	5	4	3	2	1
g. Call another person on the telephone, including selecting the correct phone number and dialing?	5	4	3	2	1

St

The following questions ask about activities you might do during a typical day.

5. In the past 2 weeks, how difficult was it to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a. Cut your food with a knife and fork?	5	4	3	2	1
b. Dress the top part of your body?	5	4	3	2	1
c. Bathe yourself?	5	4	3	2	1
d. Clip your toenails?	5	4	3	2	1
e. Get to the toilet on time?	5	4	3	2	1
f. Control your bladder (not have an accident)?	5	4	3	2	1
g. Control your bowels (not have an accident)?	5	4	3	2	1
h. Do light household tasks/chores (e.g. dust, make a bed, take out garbage, do the dishes)?	5	4	3	2	1
i. Go shopping?	5	4	3	2	1
j. Do heavy household chores (e.g. vacuum, laundry or yard work)?	5	4	3	2	1

The following questions are about your ability to be mobile, at home and in the community.

6. In the past 2 weeks, how difficult was it to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a. Stay sitting without losing your balance?	5	4	3	2	1
b. Stay standing without losing your balance?	5	4	3	2	1
c. Walk without losing your balance?	5	4	3	2	1
d. Move from a bed to a chair?	5	4	3	2	1
e. Walk one block?	5	4	3	2	1
f. Walk fast?	5	4	3	2	1
g. Climb one flight of stairs?	5	4	3	2	1
h. Climb several flights of stairs?	5	4	3	2	1
i. Get in and out of a car?	5	4	3	2	1

The following questions are about your ability to use your hand that was MOST AFFECTED by your stroke.

7. In the past 2 weeks, how difficult was it to use your hand that was most affected by your stroke to...	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
a. Carry heavy objects (e.g. bag of groceries)?	5	4	3	2	1
b. Turn a doorknob?	5	4	3	2	1
c. Open a can or jar?	5	4	3	2	1
d. Tie a shoe lace?	5	4	3	2	1
e. Pick up a dime?	5	4	3	2	1

The following questions are about how stroke has affected your ability to participate in the activities that you usually do, things that are meaningful to you and help you to find purpose in life.

8. During the past 4 weeks, how much of the time have you been limited in...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Your work (paid, voluntary or other)	5	4	3	2	1
b. Your social activities?	5	4	3	2	1
c. Quiet recreation (crafts, reading)?	5	4	3	2	1
d. Active recreation (sports, outings, travel)?	5	4	3	2	1
e. Your role as a family member and/or friend?	5	4	3	2	1
f. Your participation in spiritual or religious activities?	5	4	3	2	1
g. Your ability to control your life as you wish?	5	4	3	2	1
h. Your ability to help others?	5	4	3	2	1

SIS V3.0, SIS-16 and SIS-16 Proxy version

Stroke Impact Scale

Scaling and Scoring

Version 3.0: May 2011

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Dissemination

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The SIS is composed of 59 items investigating 8 domains.

Domains and Clusters

Domains	Number of Items	Cluster of Items	Item reversion	Direction of Domains
Strength	4	1a-1d	No	Low score = High impact on QOL
Hand function	5	7a-7e	No	
Mobility	9	6a-6i	No	
Activities of daily living	10	5a-5j	No	
Emotion	9	3a-3e, 3g 3f, 3h, 3i	No Yes	
Memory	7	2a-2g	No	
Communication	7	4a-4g	No	
Social participation	8	8a-8h	No	
Stroke recovery	1	9	Not Applicable	

Item 9 (Stroke recovery) does not belong to any of the dimensions.

Scoring of Domains

Item scaling	5-point scale from 1 to 5
Weighting of items	No
Range of scores	0-100
Scoring Procedure	• <u>Scores by dimension (except for Stroke recovery):</u> Final score = [(Raw score –Min)/(Max-Min)] * 100 With Min=1; Max =5 Raw score = Mean of non-missing items • <u>Stroke recovery</u>: Final score = item score • <u>Emotion domain score</u> There are 3 items that change polarity in the emotion domain,

	3f, 3h, and 3l. The SIS scoring database takes this change of direction into account when scoring, however, if you are scoring manually, you must reverse the scores, i.e 1 becomes 5, 2 becomes 4, 3 remains the same, 4 becomes 2, and 5 becomes 1, prior to manual calculation. For these items, use the following equation to compute the individual's score: Item score = 6 – individual's rating • **Physical domain score**: Strength, Hand function, Mobility and Activities of daily living may be combined into one Physical domain: Physical domain score = Mean of final scores of the four domains
Interpretation and Analysis of missing data	• For a particular subject, if ≥ 50% of the items in a dimension are missing then the domain score is missing • If less than 50% item responses are missing in a dimension: Score = [(Mean –Min)/(Max-Min)] * 100 Score = Dimension score for a particular dimension Mean = Mean of non-missing item scores within that dimension With Min=1; Max =5
Interpretation and Analysis of 'non-concerned' answers	**Question 1**: If patient says, "I don't have an affected side", then instruct them to score using their perceived weaker side. If they still insist there is no affected, or weaker, side instruct them to score using their dominant side. **Question 4**: If patient says s/he does not do any or all of the items listed, code item(s) as Extremely Difficult. (Item f) If patient does not call but is handed the phone this is OK. (Item g) If patient cannot hold a phone book, if they can read it this is OK. This item addresses whether the patient is able to initiate a phone call, look up the number, and dial this number correctly. **Question 5**: If patient says s/he does not do any or all of the items listed, code item(s) as Cannot do at all. (Item a) If person is on pureed food, even if they feel they could cut the food, code as Cannot do at All (Item c) Bathing oneself does not include getting into the tub. (Item e) This question is associated with movement. Does the person have the physical ability to get to the bathroom quickly enough? (Item f) Losing a little urine/dribbling is considered an accident. If person has intermittent catheter and is having no leaking problems code them as per report If person has an in-dwelling Foley catheter, code as Cannot do at all. (Item g) Constipation is not counted here person has to have an accident. (Item i) "Shopping" means any type of shopping and does not include driving.

	Question 6: If patient hasn't done any of the items in the past two weeks code as Cannot do at all. (Item h) If patient hasn't "climbed several flights of stairs" in two weeks, they may be prompted by saying "have you gone up and down one flight of stairs a couple of times in a row." If they still say they have not done it then they must be coded as Cannot do at all. (Item i) If the patient wants to know what kind of car say "your car" or "the car you ride in most." **Question 7**: If patient says "I don't have an affected side", then instruct them to score using their perceived weaker side. If they still insist there is no affected, or weaker, side instruct them to score using their dominant side. (Item a) If the patient says s/he has not been to the grocery store say "have you carried anything heavy with that hand." (Item d) This item is to tie a shoelace/bow using both hands. **Question 8**: If patient does not do any of the specific items (and has never done), code interference as None of the time.

The SIS-16 is composed of 16 items investigating 3 domains.

Domains and Clusters

Domains	Number of Items	Cluster of Items	Item reversion	Direction of Domains
Hand function	1	p	No	Low score = High impact on QOL
Mobility	7	i-o	No	
Activities of daily living	8	a-h	No	

Scoring of Domains

Item scaling	5-point scale from 1 to 5
Weighting of items	No
Range of scores	0-100
Scoring Procedure	**Score by domain:** Final score = [(Raw score –Min)/(Max-Min)] * 100 With Min=1; Max =5 Raw score = Mean of non-missing items

Interpretation and Analysis of missing data	• For a particular subject, if ≥ 50% of the items in a dimension are missing then the domain score is missing • If less than 50% item responses are missing in a dimension: Score = [(Mean –Min)/(Max-Min)] * 100 Score = Dimension score for a particular dimension Mean = Mean of non-missing item scores within that dimension With Min=1; Max =5

REFERENCE(S):

From the Stroke Impact Scale Version 3.0 Guide for Administration

E.4.6 Hospital anxiety and depression scale

HADS Questionnaire:HADS Questionnaire 26/6/13 13:12 Page 1

Hospital Anxiety and Depression Scale (HADS)

GL assessment
the measure of potential

Name: ______________________ Date: ____________

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and underline the reply which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A	D	
		I feel tense or 'wound up'
3		Most of the time
2		A lot of the time
1		From time to time, occasionally
0		Not at all
		I still enjoy the things I used to enjoy
	0	Definitely as much
	1	Not quite so much
	2	Only a little
	3	Hardly at all
		I get a sort of frightened feeling as if something awful is about to happen
3		Very definitely and quite badly
2		Yes, but not too badly
1		A little, but it doesn't worry me
0		Not at all
		I can laugh and see the funny side of things
	0	As much as I always could
	1	Not quite so much now
	2	Definitely not so much now
	3	Not at all
		Worrying thoughts go through my mind
3		A great deal of the time
2		A lot of the time
1		Not too often
0		Very little
		I feel cheerful
	3	Never
	2	Not often
	1	Sometimes
	0	Most of the time
		I can sit at ease and feel relaxed
0		Definitely
1		Usually
2		Not often
3		Not at all

	A	D
I feel as if I am slowed down		
Nearly all the time		3
Very often		2
Sometimes		1
Not at all		0
I get a sort of frightened feeling like 'butterflies' in the stomach		
Not at all	0	
Occasionally	1	
Quite often	2	
Very often	3	
I have lost interest in my appearance		
Definitely		3
I don't take as much care as I should		2
I may not take quite as much care		1
I take just as much care as ever		0
I feel restless as if I have to be on the move		
Very much indeed	3	
Quite a lot	2	
Not very much	1	
Not at all	0	
I look forward with enjoyment to things		
As much as I ever did		0
Rather less than I used to		1
Definitely less than I used to		2
Hardly at all		3
I get sudden feelings of panic		
Very often indeed	3	
Quite often	2	
Not very often	1	
Not at all	0	
I can enjoy a good book or radio or television programme		
Often		0
Sometimes		1
Not often		2
Very seldom		3

Now check that you have answered all the questions

	A	D
TOTAL		

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E.4.7 Permissions

Stroke Impact Scale

Dear Lisa,

I am pleased to confirm that we received your payment. Consequently, please find attached the requested language version along with the scoring manual.

I remind you that this version is a 2.0 version, not a 3.0 version. In order to create version 3.0 you will simply need to delete items 2e, 5j, 5k, 6e, and 8g. We hope you will perform these changes and use version 3.0 of the SIS in your research so that all current research using the SIS employs the same version.

The User Agreement is the proof you have permission to use the SIS.

Best regards,

Valérie

Valérie Lavenir
Information Resources Specialist

PROs & ClinROs Information Support Unit

Generally out of the office on Friday afternoons

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Hospital anxiety and depression scale

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hereto the day and year first above written

Signed on behalf of GL Assessment Limited

9/12/2013

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Appendix F

Intervention Monitoring Forms

F.1 Case record form- Treatment session

SUMMARY OF ASSESSMENT/TREATMENT SESSION

Lab Assessments Done

- ☐ Lab Sheet |__|
- ☐ Modified Ashworth Scale |__|
- ☐ MMSE |__|
- ☐ TMS Questionnaire |__|
- ☐ TMS Assessments
- ☐ Action Research Arm Test |__|
- ☐ Fugl-Meyer upper limb assessment |__|
- ☐ Modified Tardieu Scale |__|
- ☐ Stroke Impact Scale|__|
- ☐ Motor Activity Log |__|
- ☐ Adverse Events.
- ☐ If Serious Adverse Event Occurred, Sponsor & Ethics Committee notified within specified time frame/tDCS Questionniare|__|
- ☐ News since last meeting questionnaire |__|

Researcher's Signature: Date: |__|__| |__|__| | 2 | 0 | | |

D D M M Y Y Y Y

I have personally reviewed all data recorded for this visit and found them to be complete and accurate.

PI's Signature: Date: |__|__| |__|__| | 2 | 0 | | |

D D M M Y Y Y Y

NEWS SINCE LAST MEETING

How are you feeling today?

....

....

....

....

Have you had any general health problems (common cold, back-pains, etc.) since last meeting?

If yes – what kind, when, and are you recovered?

....

....

....

....

Any change in medication?

…………………………………………………………………………………………

…………………………………………………………………………………………

……………………………………………………

Have you had any problems after the last session?

....

....

....

Have you been able to perform the intensive exercises/therapy?

....

....

....

....

Are you happy with your participation in this study?

....

....

....

Is there anything else you would like to talk about?

....

....

....

F.2 tDCS questionnaire

Subject code: ____ **Date:**____/____/____

Experiment: ____

Have you experienced any sensation during the direct current stimulation? Please answer to the following questions regarding the different sensations, indicating the degree of intensity of your perception according to the following scale:

- ***None*** **= I have not felt the described sensation**
- ***Mild*** **= I have mildly felt the described sensation**
- ***Moderate*** **= I have felt the described sensation**
- ***Considerable*** **= I have felt the described sensation to a considerable degree**
- ***Strong*** **= I have strongly felt the described sensation**

In the first stimulation block

Itchiness:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong
Pain:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong
Burning:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong
Warmth/Heat:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong
Pinching:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong
Iron taste:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong
Fatigue:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong
Other________________:	□ None	□ Mild	□ Moderate	□ Considerable	□ Strong

When did the sensations begin?

□ At the beginning of the block □ About the middle of the block □ Towards the end of the block

How long did they last?

□ They stopped soon □ They stopped in the middle of the block □ They stopped at the end of the block

How much did these sensations affect your performance?

□ Not at all □ A little □ Considerably □ Much □ Very much

In the second stimulation block

...

If you want to provide more details, please briefly describe the experimented sensations in relation to:

- Itchiness:
- Pain:
- Burning:
- Warmth/Heat:
- Pinching:
- Iron taste:
- Fatigue:
- Other:

Appendix G

Interview Guide

G.1 Interview guide for pilot Interview

Interview Questions

*(*Questions will be asked to all the participants receiving sham or real stimulation since all will be receiving some form of brain stimulation)*

A. Taking part in the research

1. What are your overall thoughts about taking part in this research?

Guided Questions

a) Did you experience any difficulties travelling to the university from your home?

b) Do you think you had enough sessions of robot therapy and brain stimulation?

c) Were the assessment sessions (first and last session) too long?

d) Were the treatment sessions too short?

e) Did you receive enough support from the researchers at the university?

B. Robot therapy and Non-Invasive Brain Stimulation Effectiveness

1. Did you feel any different about your everyday life during or after the trial? (open)

2. Did you feel any differences in your activities immediately after brain stimulation? (open)*

3. Guided Questions

a) I am now more aware of my affected arm

(Likert Scale: Strongly agree, agree, neutral, disagree, strongly disagree

b) My arm feels weaker

(Strongly agree, agree, neutral, disagree, strongly disagree)

c) My arm feels tighter (Likert)

(Strongly agree, agree, neutral, disagree, strongly disagree)

d) I can reach out with my arm more easily (Likert)

(Strongly agree, agree, neutral, disagree, strongly disagree)

e) I can now pick up objects (Likert)

(Strongly agree, agree, neutral, disagree, strongly disagree)

f) Are you now able to do things that you could not do before? YES / NO Please give examples

g) Are you now able to do things better than you could before? YES / NO Please give examples

h) Can you now perform any two handed tasks more easily? YES / NO Please give examples

C. System Usability

Robot

a) I did not find the treatment enjoyable (Likert)

(Strongly agree, agree, neutral, disagree, strongly disagree)

b) It was easy to understand what I had to do (Likert)

(Strongly agree, agree, neutral, disagree, strongly disagree)

c) The target during the robot assessments and games was easy to see (Likert)

(Strongly agree, agree, neutral, disagree, strongly disagree)

d) I did not understand the graphs showing my performance (Likert)

(Strongly agree, agree, neutral, disagree, strongly disagree)

*Brain Stimulation**

a) The stimulation was uncomfortable (Likert) (this question will be asked for people who received real tDCS)

(Strongly agree, agree, neutral, disagree, strongly disagree)

b) The pads placed on my head were comfortable

(Strongly agree, agree, neutral, disagree, strongly disagree)

c) The bandage placed around the electrodes was uncomfortable

(Strongly agree, agree, neutral, disagree, strongly disagree)

d) The sensation of the magnet coil on top of your head was painful

(Strongly agree, agree, neutral, disagree, strongly disagree)

e) How do you think the non-invasive brain equipment could be improved? (open)

D. General Questions

a) What were the best and worst aspects of the non-invasive brain stimulation? (open)*

b) What were the best and worst aspects of the robot therapy? (open)

c) If you had the opportunity, would you use the robot again? (open)

d) If you had the opportunity, would you undergo non-invasive brain stimulation again? (open)

e) How could robot therapy and non-invasive brain stimulation be improved? (open)*

f) Would you recommend robot therapy and non-invasive brain stimulation to other people who have had a stroke? (open)*

g) Is there anything else you would like to add? (Open)

G.2 Amended interview guide after pilot interview

Interview Questions

*(*Questions will be asked to all the participants receiving sham or real stimulation since all will be receiving some form of brain stimulation)*

A. Taking part in the research

1. What are your overall thoughts about taking part in this research?

Guided Questions

a) Did you experience any difficulties travelling to the university from your home?
b) Do you think you had enough sessions of robot therapy and brain stimulation?
c) Were the assessment sessions (first and last session) too long?
d) Were the treatment sessions too short?
e) Did you receive enough support from the researchers at the university?

B. Robot therapy and Non-Invasive Brain Stimulation Effectiveness

1. Did you feel any different about your everyday life during or after the trial? (open)
2. Did you feel any differences in your activities immediately after brain stimulation? (open)*

3. Guided Questions

a) I am now more aware of my affected arm

(Likert Scale: Strongly agree, agree, neutral, disagree, strongly disagree

b) After the research study, my arm feels weaker

(Strongly agree, agree, neutral, disagree, strongly disagree)

c) My arm feels less tighter (Likert)

(Strongly agree, agree, neutral, disagree, strongly disagree)

d) I can reach out with my arm more easily (Likert)

(Strongly agree, agree, neutral, disagree, strongly disagree)

e) I can now pick up objects (Likert)
(Strongly agree, agree, neutral, disagree, strongly disagree)

f) Are you now able to do things that you could not do before? YES / NO Please give examples
g) Are you now able to do things better than you could before? YES / NO Please give examples
h) Can you now perform any two handed tasks more easily? YES / NO Please give examples

C. System Usability

Robot
a) I did not find the treatment enjoyable (Likert)
(Strongly agree, agree, neutral, disagree, strongly disagree)

b) It was easy to understand what I had to do (Likert)
(Strongly agree, agree, neutral, disagree, strongly disagree)

c) The target during the robot assessments and games was easy to see (Likert)
(Strongly agree, agree, neutral, disagree, strongly disagree)

d) The games chosen were beneficial for my weak arm
(Strongly agree, agree, neutral, disagree, strongly disagree)

e) I understood the graphs showing my performance (Likert)
(Strongly agree, agree, neutral, disagree, strongly disagree)

*Brain Stimulation**

a) The stimulation was comfortable (Likert) (this question will be asked for people who received real tDCS)

(Strongly agree, agree, neutral, disagree, strongly disagree)

b) The pads placed on my head were comfortable
(Strongly agree, agree, neutral, disagree, strongly disagree)

c) The bandage placed around the electrodes was comfortable
(Strongly agree, agree, neutral, disagree, strongly disagree)

d) The sensation of the magnet coil on top of your head was painful
(Strongly agree, agree, neutral, disagree, strongly disagree)

e) How do you think the non-invasive brain equipment could be improved?
(open)

D. General Questions

a) What were the best and worst aspects of the non-invasive brain stimulation? (open)*
b) What were the best and worst aspects of the robot therapy? (open)
c) If you had the opportunity, would you use the robot again? (open)
d) If you had the opportunity, would you undergo non-invasive brain stimulation again? (open)
e) How could robot therapy and non-invasive brain stimulation be improved? (open)*
f) Would you recommend robot therapy and non-invasive brain stimulation to other people who have had a stroke? (open)*
g) Is there anything else you would like to add? (Open)

Appendix H

Data and Statistics

H.1 RCT Screening measures results

Table H.1 Results of screening procedure illustrating the median and the min/max score for each test of each sub-acute participant that completed the trial

Participant	MAS*	MRC**
P01	Median: 1.5 Min/Max: 1,2	Median: 3 Min/Max: 2,3
P02	Median: 0 Min/Max: 0,1	Median: 4 Min/Max: 4,4
P03	Median: 0 Min/Max: 0,0	Median: 4 Min/Max: 4,4
P04	Median: 0 Min/Max: 0,1	Median: 2 Min/Max: 2,3
P05	Median: 0 Min/Max: 0,1	Median: 2 Min/Max: 0,3
P06	Median: 0 Min/Max: 0,2	Median: 3 Min/Max: 2,3
P07	Median: 0 Min/Max: 0,1	Median: 3.5 Min/Max: 3,4
P08	Median: 0 Min/Max: 0,0	Median: 4 Min/Max: 3,4
P09	Median: 0.5 Min/Max: 1,0	Median: 4 Min/Max: 3,4
P10	Median: 0 Min/Max: 0	Median: 4 Min/Max: 3,4
P11	Median: 1.5 Min/Max: 1,2	Median: 2 Min/Max: 0,2
P12	Median: 2 Min/Max: 2,2	Median: 3 Min/Max: 2,4
Overall Median and Min/Max	**0 (0,2)**	**3.25 (2,4)**

***MAS=Modified Ashworth Scale/Score out of 5/ Median of 12 muscles tested;**

****MRC=Medical Research Council for Muscle Strength/Score out of 5/ Median of 12 muscles tested**

Table H.2 Results of screening procedure illustrating the median and the min/max scores for each test of each chronic participant that completed the trial

Participant	MAS*	MRC**
CP1	Median: 2 Min/Max: 2,3	Median: 3 Min/Max: 2,4
CP2	Median: 0 Min/Max:0,1	Median: 3 Min/Max: 2,4
CP3	Median: 1 Min/Max: 0,1	Median: 3 Min/Max: 2,4
CP4	Median: 1 Min/Max:1,2	Median: 3 Min/Max: 3,4
CP5	Median: 0.5 Min/Max: 0,2	Median: 3 Min/Max: 3,4
CP6	Median: 0.5 Min/Max:0,2	Median: 3 Min/Max: 3,4
CP7	Median: 1 Min/Max:0,1	Median: 3 Min/Max: 3,4
CP8	Median: 2 Min/Max:1,3	Median: 3 Min/Max: 0,4
CP9	Median: 2 Min/Max:1,2	Median: 2 Min/Max: 1,3
CP10	Median:1.5 Min/Max:1,2	Median: 3 Min/Max: 2,3
Overall Median and Min/Max	**1(0,2)**	**3(2,3)**

***MAS=Modified Ashworth Scale/Score out of 5/ Median of 12 muscles tested;**

****MRC=Medical Research Council for Muscle Strength/Score out of 5/ Median of 12 muscles tested**

H.2 RCT Clinical measures results and statistics

H.2.1 Fugl Meyer Assessment (FMA)

Data of the individual participants are presented in the tables below. These tables are followed by the statistical results.

Table H.3 FMA Scores at baseline, post-Intervention and follow-up of each sub-acute participant

Participant Number	Baseline	Post-Interven-tion	Follow-Up	Change *2	Change	Change	Change
	(B)	(P)	(F)	(P-B)	(%)	(F-B)	(%)
P01	36	42	32	+6	+9	-4	-6
P02	52	66	66	+14	+21	+14	+21
P03	59	66	66	+7	+11	+7	+11
P04	22	33	30	+11	+17	+8	+12
P05	4	11	10	+7	+11	+6	+9
P06	40	50	57	+10	+15	+17	+26
P07	46	59	62	+13	+20	+16	+24
P08	59	64	61	+5	+8	+2	+3
P09	49	56	55	+7	+11	+6	+9
P10	39	52	56	+13	+20	+17	+26
P11	8	21	31	+13	+20	+23	+35
P12	26	43	41	+17	+26	+15	+23
Mean (SD)*3	**36.67 (18.36)**	**49.92 (17.78)**	**47.25 (18.00)**	**10.25 (3.82)**	**15.75 (5.74)**	**10.58 (7.66)**	**16.08 (11.64)**

***1 FMA= Fugl-Meyer Assessment/ Maximum Score is 66**

***2 Change=% from the Maximum Score**

Table H.4 FMA scores at baseline, post-Intervention and follow-up of each chronic participant

Participant Number	Baseline	Post-Interven-tion	Follow-Up	Change*[2]	Change	Change	Change
	(B)	(P)	(F)	(P-B)	(%)	(F-B)	(%)
CP1	19	19	23	0	0	+4	+6
CP2	23	23	22	0	0	-1	-2
CP3	23	35	24	+12	+18	+1	+2
CP4	17	23	24	+6	+9	+7	+11
CP5	28	37	41	+9	+14	+13	+20
CP6	37	43	44	+6	+9	+7	+11
CP7	32	42	36	+10	+15	+4	+6
CP8	8	14	8	+6	+9	0	0
CP9	22	26	18	+4	+6	-4	-6
CP10	33	38	32	+5	+8	-1	-2
Mean (SD)*[3]	**4.6 (7.82)**	**24.2 (8.60)**	**30.0 (10.23)**	**27.2 (11.01)**	**5.8 (3.91)**	**8.8 (5.90)**	**3.0 (5.03)**

***1 FMA= Fugl-Meyer Assessment/ Maximum Score is 66;**

***2 Change=% from the Maximum Score**

Table H.5 Repeated measures ANOVA of FMA baseline, post-intervention and follow-up

Tests of Within-Subjects Effects						
Measure: MEASURE_1						
Source		Type III Sum of Squares	df	Mean Square	F	Sig.
factor1	Sphericity Assumed	878.576	2	439.288	25.248	.000
	Greenhouse-Geisser	878.576	1.416	620.532	25.248	.000
	Huynh-Feldt	878.576	1.488	590.292	25.248	.000
	Lower-bound	878.576	1.000	878.576	25.248	.000

Table H.6 Post-Hoc Analysis of FMA: Paired Samples t-test

		Paired Differences					Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		
					Lower	Upper	
Pair 1	FMA_baseline - FMA_Post	-8.2272	4.39623	.93728	-10.176	-6.2780	.000
Pair 2	FMA_baseline - FMA_Three month	-7.1363	7.51694	1.60262	-10.469	-3.8035	.000

H.2.2 Action Research Arm Test (ARAT)

Data of the individual participants of the Action Research Arm Test are presented below. This is followed by the statistical results.

Table H.7 ARAT Scores at baseline, post-Intervention and follow-up of each sub-acute participant

Participant Number	Baseline (B)	Post-Interven-tion (P)	Follow-Up (F)	Change*2 (P-B)	Change (%)	Change (F-B)	Change (%)
P01	6	29	30	+23	+40	+24	+42
P02	54	55	57	+1	+2	+3	+5
P03	56	56	57	0	0	+1	+2
P04	7	19	19	+12	+21	+12	+21
P05	0	0	0	0	0	0	0
P06	33	47	55	+14	+25	+22	+39
P07	43	54	54	+11	+19	+11	+19
P08	50	57	57	+7	+12	+7	+12
P09	34	50	47	+16	+28	+13	+23
P10	35	54	53	+19	+33	+18	+32
P11	3	7	5	+4	+7	+2	+4
P12	16	23	28	+7	+12	+12	+21
Median (min,max)*3	33.5 (0,56)	48.5 (0,57)	50.0 (0,57)	9.0 (0,23)	15.5 (0,40)	11.5 (0,25)	20.0 (0,42)

***1 Action Research Arm Test/Maximum Score is 57 *2 Change=% from the Maximum Score**

Table H.8 ARAT Scores at baseline, post-Intervention and follow-up of each chronic participant

Participant Number	Baseline (B)	Post-Interven-tion (P)	Follow-Up (F)	Change*[2] (P-B)	Change (%)	Change (F-B)	Change (%)
CP1	3	3	5	0	0	+2	+4
CP2	7	8	9	+1	+2	+2	+4
CP3	4	8	7	+4	7	+3	+5
CP4	6	6	8	0	0	+2	+4
CP5	8	8	8	0	0	0	0
CP7	11	14	13	+3	+5	+2	+4
CP8	16	18	13	+2	+4	-3	-5
CP9	0	0	0	0	0	0	0
CP10	3	3	3	0	0	0	0
Median (Min, Max)*[3]	6.0 (0,16)	8.0 (0,18)	8.0 (0,13)	0 (0,4)	0 (0,7)	2 (-3,3)	4 (-5,5)

***1 Action Research Arm Test/Maximum Score is 57**

***2 Change=% from the Maximum Score**

Table H.9 Friedman's repeated measures ANOVA to ARAT scores at baseline, post-intervention and follow-up

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distributions of ARAT_baseline, ARAT_post and ARAT_threemonth are the same.	Related-Samples Friedman's Two-Way Analysis of Variance by Ranks	.000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

Table H.10 Wilcoxon signed rank test to ARAT baseline and post-intervention scores

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The median of differences between ARAT_baseline and ARAT_post equals 0.	Related-Samples Wilcoxon Signed Rank Test	.001	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

Table H.11 Wilcoxon signed rank test to ARAT baseline and follow-up scores

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The median of differences between ARAT_baseline and ARAT_threemonth equals 0.	Related-Samples Wilcoxon Signed Rank Test	.004	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

Table H.12 Linear regression model of ARAT post-intervention scores

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-.804	6.726		-.120	.906
	ARAT_baseline	.894	.122	.770	7.306	.000
	Real_Sham	-4.754	4.355	-.110	-1.092	.292
	time_since_stroke	-.068	.069	-.077	-.982	.342
	Cortical_subcortical	6.709	4.166	.151	1.610	.128
	ARATxrs	.111	.173	.066	.640	.532

a. Dependent Variable: ARAT_post

Table H.13 Linear Regression model to ARAT follow-up scores

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	3.520	8.211		.429	.674
	ARAT_baseline	.914	.149	.761	6.120	.000
	Real_Sham	-5.483	5.316	-.123	-1.031	.319
	time_since_stroke	-.106	.085	-.117	-1.254	.229
	Cortical_subcortical	4.194	5.086	.091	.825	.422
	ARATxrs	.178	.211	.103	.845	.412

a. Dependent Variable: ARAT_threemonth

H.2.3 Modifed tardieu scale (MTS)

The data of MTS of the individual participants are presented in the tables below. This is followed by the statistical results.

Table H.14 MTS* Quality of movement at baseline, post-Intervention and follow-up of sub-acute participants

MTS Quality of movement rated between 0-5		Baseline	Post-Intervention	Follow-Up	Change	Change
		(B)*	(P)	(F)	(P-B)	(F-B)
P01	Elbow Flexors	1	2	2	+1	+1
	Wrist Flexors	2	2	2	0	0
P02	Elbow Flexors	0	0	0	0	0
	Wrist Flexors	1	0	0	-1	-1
P03	Elbow Flexors	0	0	0	0	0
	Wrist Flexors	0	0	0	0	0
P04	Elbow Flexors	2	2	1	0	-1
	Wrist Flexors	2	2	1	0	-1
P05	Elbow Flexors	1	1	2	0	+1
	Wrist Flexors	1	0	2	-1	+1
P06	Elbow Flexors	0	0	0	0	0
	Wrist Flexors	1	0	0	-1	0
P07	Elbow Flexors	2	0	0	-2	-2
	Wrist Flexors	0	0	0	0	0
P08	Elbow Flexors	0	0	0	0	0
	Wrist Flexors	0	0	0	0	0
P09	Elbow Flexors	1	1	1	0	0
	Wrist Flexors	0	1	1	+1	+1
P10	Elbow Flexors	0	0	0	0	0
	Wrist Flexors	0	0	0	0	0
P11	Elbow Flexors	2	2	2	0	0
	Wrist Flexors	1	2	2	+1	+1
P12	Elbow Flexors	2	2	2	0	0
	Wrist Flexors	2	2	2	0	0
Median (Min, Max)	Elbow Flexors	1 (0,2)	0 (0,2)	0 (0,2)	0 (-2,1)	0 (-2,1)
	Wrist	1	0	0	0	0

	Flexors	(0,2)	(0,2)	(0,2)	(-1,1)	(-1,1)

Table H.15 MTS* Quality of movement at baseline, post-Intervention and follow-up of chronic participants

Participant		Baseline	Post-Intervention	Follow-Up	Change	Change
		(B)*	(P)	(F)	(P-B)	(F-B)
CP1	Elbow Flexors	2	3	1	+1	-1
	Wrist Flexors	2	2	2	0	0
CP2	Elbow Flexors	1	1	1	0	0
	Wrist Flexors	0	1	1	+1	+1
CP3	Elbow Flexors	1	3	1	+2	0
	Wrist Flexors	1	3	0	+2	-1
CP4	Elbow Flexors	1	1	1	0	0
	Wrist Flexors	1	1	1	0	0
CP5	Elbow Flexors	1	1	1	0	0
	Wrist Flexors	1	0	1	-1	0
CP6	Elbow Flexors	1	0	1	-1	0
	Wrist Flexors	3	2	1	-1	-2
CP7	Elbow Flexors	1	1	1	0	0
	Wrist Flexors	2	2	1	0	-1
CP8	Elbow Flexors	2	2	2	0	0
	Wrist Flexors	2	2	2	0	0
CP9	Elbow Flexors	3	2	2	-1	-1
	Wrist Flexors	3	2	2	-1	-1
CP10	Elbow Flexors	2	2	1	0	-1
	Wrist Flexors	0	2	2	+2	+2
Median (IQR)	Elbow Flexors	1 (1,3)	1 (0,3)	1 (1,2)	0 (-1,2)	0 (-1,0)
	Wrist Flexors	2 (0,3)	2 (0,3)	1 (0,2)	0 (-1,2)	0 (-2,2)

* MTS Quality of movement rated between 0-5

Table H.16 MTS angle of catch at fast velocity of the sub-acute participants

Participant		Baseline (º)	Post-Intervention (º)	Follow-Up (º)	Change	Change
		(B)*	(P)	(F)	(P-B)	(F-B)
P01	Elbow Flexors	97	92.5	100	+4.5	+3.0
	Wrist Flexors	5	45	30	+40	+15
P02	Elbow Flexors	No catch	20	No catch	+20	No catch
	Wrist Flexors	24	No catch	No catch	-24	-24
P03	Elbow Flexors	No catch	No catch	No catch	No catch	No catch
	Wrist Flexors	No catch	No catch	No catch	No catch	No catch
P04	Elbow Flexors	30	77	43	+47	+13
	Wrist Flexors	11	No catch	No catch	-11	-11
P05	Elbow Flexors	No catch	No catch	53	No catch	+53
	Wrist Flexors	No catch	No catch	34	No catch	+34
P06	Elbow Flexors	No catch	No catch	No catch	No catch	No catch
	Wrist Flexors	No catch	No catch	No catch	No catch	No catch
P07	Elbow Flexors	98	No catch	No catch	-98	-98
	Wrist Flexors	No catch	No catch	No catch	No catch	No catch
P08	Elbow Flexors	No catch	No catch	No catch	No catch	No catch
	Wrist Flexors	No catch	20	No catch	+20	No catch
P09	Elbow Flexors	11	15	15	+4	+4
	Wrist Flexors	40	40	55	No catch	+15
P10	Elbow Flexors	No catch	No catch	No catch	No catch	No catch
	Wrist Flexors	No catch	21	No catch	+21	No catch
P11	Elbow Flexors	10	45	53	+35	+43
	Wrist Flexors	No catch	30	10	+30	+10
P12	Elbow Flexors	39	45	107	+6	+68
	Wrist Flexors	45	30	40	-15	-5.0
Mean (SD)	Elbow Flexors	47.5 (40.3)	49.0 (30.7)	61.8 (35.2)	+4.81 (44.3)	+12.3 (54.8)
	Wrist Flexors	25 (17.5)	31.0 (10.0)	33.8 (16.4)	+8.7 (24.9)	+4.9 (19.4)

Table H.17 MTS angle of catch at fast velocity of the chronic participants

Participant		Baseline (º)	Post-Intervention (º)	Follow-Up (º)	Change	Change
		(B)*	(P)	(F)	(P-B)	(F-B)
CP1	Elbow Flexors	70	130	45	+60	-25
	Wrist Flexors	15	35	40	+20	+25
CP2	Elbow Flexors	94	95	109	+1	+15
	Wrist Flexors	No catch	30	No catch	+30	No catch
CP3	Elbow Flexors	40	25	25	-15	-15
	Wrist Flexors	11	25	25	+14	+14
CP4	Elbow Flexors	No catch	85	98	+85	+98
	Wrist Flexors	40	No catch	No catch	-40	-40
CP5	Elbow Flexors	No catch	No catch	No catch	No catch	No catch
	Wrist Flexors	No catch	No catch	No catch	No catch	No catch
CP6	Elbow Flexors	35	45	135	+10	+100
	Wrist Flexors	25	20	35	-5	+10
CP7	Elbow Flexors	No catch	35	0	+35	+35
	Wrist Flexors	24	No catch	25	-24	+1
CP8	Elbow Flexors	65	57	45	+8	-20
	Wrist Flexors	10	21	No catch	+11	-10
CP9	Elbow Flexors	75	50	60	-25	-15
	Wrist Flexors	15	30	30	+15	+15
CP10	Elbow Flexors	78	65	58	+13	-20
	Wrist Flexors	No catch	30	-14	+30	-14
Mean (SD)	Elbow Flexors	42.1 (36.1)	65.2 (33.0)	71.9 (37.8)	19.1 (35.3)	17.0 (50.4)
	Wrist Flexors	15.6 (12.7)	27.3 (5.5)	23.5 (19.3)	5.7 (24.1)	0.1 (20.8)

Table H.18 Friedman's repeated measures ANOVA for MTS qualtiy of movement of elbow flexors muscles

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distributions of MTS_qual_elbow_bas, MTS_qual_elbow_post and MTS_qual_elbow_fu are the same	Related-Samples Friedman's Two-Way Analysis of Variance by Ranks	.507	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

Table H.19 Friedman's repeated measures ANOVA for MTS qualtiy of movement of wrist flexor muscles

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distributions of MTS_qual_wrist_bas, MTS_qual_wrist_post and MTS_qual_fu are the same	Related-Samples Friedman's Two-Way Analysis of Variance by Ranks	.629	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05

Table H.20 Repeated measures ANOVA for MTS angle of catch of elbow flexors at baseline, post-intervention and follow-up

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
factor1	Sphericity Assumed	976.931	2	488.465	.715	.500
	Greenhouse-Geisser	976.931	1.572	621.554	.715	.471
	Huynh-Feldt	976.931	1.788	546.273	.715	.486
	Lower-bound	976.931	1.000	976.931	.715	.416
Error(factor1)	Sphericity Assumed	15020.236	22	682.738		
	Greenhouse-Geisser	15020.236	17.289	868.759		
	Huynh-Feldt	15020.236	19.672	763.537		
	Lower-bound	15020.236	11.000	1365.476		

Table H.21 Repeated measures ANOVA MTS angle of catch of wrist muscles at baseline, post-intervention and follow-up

Tests of Within-Subjects Effects
Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
factor1	Sphericity Assumed	720.095	2	360.048	3.569	.061
	Greenhouse-Geisser	720.095	1.139	632.429	3.569	.100
	Huynh-Feldt	720.095	1.228	586.342	3.569	.095
	Lower-bound	720.095	1.000	720.095	3.569	.108
Error(factor1)	Sphericity Assumed	1210.571	12	100.881		
	Greenhouse-Geisser	1210.571	6.832	177.199		
	Huynh-Feldt	1210.571	7.369	164.286		
	Lower-bound	1210.571	6.000	201.762		

H.2.5 Motor Activity Log-28 (MAL)

The individual data of the participants of MAL are presented in the table below. This is followed by the statistical results

Table H.22 MAL at Baseline, Post-Intervention and follow-up perceived by sub-acute participants

Participant	Baseline	Post-Intervention	Follow-Up	Change	Change
	(B)*	(P)	(F)	(P-B)	(F-B)
P01	0.33	0.44	0.74	+0.11	+0.41
P02	1.11	3.52	4.68	+2.41	+3.57
P03	3.65	4.69	4.46	+1.04	+0.81
P04	2.13	3.02	2.66	+0.89	+0.53
P05	0	0.3	0.14	+0.3	+0.14
P06	2.46	1.98	4.12	-0.48	+1.66
P07	1.25	4.23	2.98	+2.98	+1.73
P08	3.21	4.91	4.96	+1.7	+1.75
P09	0.61	1.5	1.57	+0.89	+0.96
P10	1.23	2.27	3.5	+1.04	+2.27
P11	0	0.09	0.27	+0.09	+0.27
P12	0	0.59	0.84	+0.59	+0.84
Median (min, max)	1.17 (0,3.65)	2.13 (0.9,4.91)	2.82 (0.14,3.96)	0.89 (0.48,2.98)	0.90 (0.14,3.57)

Table H.23 MAL at Baseline, post-intervention and at follow-up perceived by chronic participants

Participant	Baseline	Post-Intervention	Follow-Up	Change	Change
	(B)*	(P)	(F)	(P-B)	(F-B)
CP1	0.25	0.32	0.21	+0.07	-0.04
CP2	0.37	0.19	0.13	-0.18	-0.24
CP3	0.32	0.25	0.98	-0.07	+0.66
CP4	0.91	0.15	0.11	-0.76	-0.8
CP5	0	0	0	0	0
CP6	0.84	2.07	2.23	1.23	+1.39
CP7	0.36	0.23	0.464	-0.13	+0.104
CP8	0	0	0	0	0
CP9	0	0	0.035	0	+0.035
CP10	1.54	1.64	1.79	+0.1	+0.25
Median (min, max)	0.34 (0,1.54)	0.21 (0,2.07)	0.17 (0.2.23)	0.0 (-0.76,1.23)	0.02 (-0.80,1.39)

Table H.24 Friedman's Anova of the MAL scores at baseline, post-intervention, follow-up

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distributions of MAL_pre, MAL_post and MAL_threemonth are the same.	Related-Samples Friedman's Two-Way Analysis of Variance by Ranks	.003	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

Table H.25 Post-hoc analysis: Wilcoxon's signed rank test of MAL baseline and post-intervention scores

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The median of differences between MAL_pre and MAL_post equals 0.	Related-Samples Wilcoxon Signed Rank Test	.015	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

Table H.26 Post-hoc analysis: Wilcoxon's signed rank test of MAL baseline and follow-up scores

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The median of differences between MAL_pre and MAL_threemonth equals 0.	Related-Samples Wilcoxon Signed Rank Test	.001	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

Table H.27 Linear regression model for MAL post-intervention scores

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.019	.845		.023	.982
	Real_Sham	-.206	.523	-.064	-.394	.699
	time_since_stroke	-.010	.009	-.144	-1.042	.314
	Cortical_subcortical	.376	.464	.113	.809	.431
	MALxrs	-.270	.376	-.146	-.718	.483
	MAL_pre	1.309	.286	.843	4.583	.000

a. Dependent Variable: MAL_post

Table H.28 Linear regression model for MAL follow-up scores

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.014	.880		.016	.987
	Real_Sham	-.214	.544	-.062	-.393	.700
	time_since_stroke	-.011	.010	-.162	-1.202	.248
	Cortical_subcortical	.527	.484	.149	1.090	.293
	MALxrs	.029	.392	.015	.074	.942
	MAL_pre	1.211	.298	.731	4.069	.001

a. Dependent Variable: MAL_threemonth

H.2.6 Stroke Impact Scale (SIS)

The SIS data of the individual participants are presented in the following tables. These are followed by the statistical results.

Table H.29 Individual scores of each domain of the SIS at baseline and post-intervention of each sub-acute participant

SIS*[1] score per domain/ Participant	Strength	Memory	Emotion	Communication	ADL/IADL	Mobility	Hand Function	Social Participation	Perceived Stroke Recovery (%)
P01 Baseline	43.75	96.43	66.67	100	52.5	61.11	25	34.38	45
P01 Post-Intervention	62.5	92.86	100	100	65	75	35	50	45
P01 Follow-Up	56.25	85.71	88.89	100	67.5	63.88	20	53.33	55
P02 Baseline	50	64.29	86.11	78.57	77.5	88.89	85	56.25	65
P02 Post-Intervention	100	75	83.33	100	97.5	97.22	100	34.38	90
P02 Follow-Up	100	89.29	72.22	96.43	97.5	97.22	100	62.5	95
P03 Baseline	50	64.29	75	67.86	45	58.33	25	40.63	25
P03 Post-Intervention	68.75	67.86	75	55.55	75	72.22	85	75	90
P03 Follow-up	75	60.71	94.44	78.57	70	66.67	65	68.75	85
P04 Baseline	62.5	100	100	96.43	20	44.44	30	37.5	70
P04 Post-Intervention	56.25	96.43	100	78.57	52.5	63.88	40	40.63	70
P04 Follow-up	56.25	89.29	94.44	89.29	37.5	80.56	5	59.38	60

SIS*[1] score per domain/ Participant	Strength	Memory	Emotion	Communication	ADL/IADL	Mobility	Hand Function	Social Participation	Perceived Stroke Recovery (%)
P05 Baseline	50	85.71	44.44	89.29	45	50	0	18.75	10
P05 Post-Intervention	37.5	67.86	55.55	96.43	35	50	5	18.75	30
P05 Follow-Up	31.25	85.7	58.33	92.86	50	66.67	30	37.5	30
P06 Baseline	37.5	100	86.11	100	50	61.11	15	50	50
P06 Post-Intervention	50	100	80.55	100	70	77.77	55	62.5	50
P06 Follow-up	62.5	100	83.33	100	72.5	80.56	70	75	70
P07 Baseline	25	89.3	69.4	85.7	47.5	63.9	25	56.25	75
P07 Post-Intervention	62.5	96.4	91.67	96.4	65	94.4	55	75	65
P07 Follow-up	68.75	96.4	97.22	96.4	70	100	50	84.4	60
P08 Baseline	56.25	50	83.33	60.71	72.5	88.89	65	50	20
P08 Post-Intervention	87.5	100	88.89	100	95	100	100	84.38	80
P08 Follow-up	93.75	96.43	83.33	100	95	94.44	100	90.62	90
P09 Baseline	56.25	96.43	80.56	96.43	70	58.33	5	68.75	35
P09 Post-Intervention	56.25	100	88.89	96.43	85	66.67	20	46.88	40
P09 Follow--up	62.5	100	86.11	100	82.5	94.44	65	100	40
P10 Baseline	43.75	50	61.11	42.86	45	58.33	20	3.13	55
P10 Post-Intervention	68.75	85.71	83.33	92.86	52.5	75	45	18.75	75

SIS*[1] score per domain/ Participant	Strength	Memory	Emotion	Communication	ADL/IADL	Mobility	Hand Function	Social Participation	Perceived Stroke Recovery (%)
P11 Baseline	25	100	86.11	100	42.5	61.11	0	37.5	30
P11 Post-Intervention	81.25	100	88.89	100	67.5	61.11	10	78.13	50
P11 Follow-up	81.25	100	97.22	100	62.5	80.56	15	81.25	20
P12 Baseline	43.75	100	61.11	96.43	37.5	44.44	0	18.75	35
P12 Post-Intervention	62.5	96.4	83.33	85.71	72.5	72.22	20	53.33	55
P12 Follow-up	56.25	96.43	83.33	89.29	57.5	75	10	31.25	60
Mean (SD) Baseline	**45.31 (11.65)**	**83.04 (20.09)**	**75.00 (15.12)**	**84.52 (18.55)**	**50.42 (16.13)**	**61.57 (14.31)**	**24.58 (26.32)**	**39.32 (18.72)**	**42.92 (20.61)**
Mean (SD) Post-Intervention	**66.15 (16.95)**	**89.88 (12.63)**	**84.95 (11.81)**	**91.83 (13.24)**	**69.38 (17.91)**	**75.46 (15.16)**	**47.50 (32.99)**	**53.14 (22.50)**	**61.67 (19.69)**
Mean (SD) Three-Month Follow-up	**68.23 (18.55)**	**87.20 (16.85)**	**85.41 (11.18)**	**94.05 (7.03)**	**69.58 (17.12)**	**81.71 (12.50)**	**48.33 (32.98)**	**63.82 (24.41)**	**61.25 (23.07)**

Table H.30 Mean scores of each domain of the SIS at baseline, post-intervention and at follow-up of the chronic group

SIS*[1] score per domain/ Participant	Strength	Memory	Emotion	Communication	ADL/IADL	Mobility	Hand Function	Social Participation	Perceived Stroke Recovery (%)
CP1 Baseline	50	46.43	80.56	85.7	57.5	77.78	5	40.63	40
CP1 Post-Intervention	56.25	85.71	61.11	85.71	50	72.22	15	25	5
CP1 Follow-Up	50	64.29	86.11	85.71	62.5	72.22	15	53.13	75
CP2 Baseline	31.25	60.71	58.33	78.57	57.5	58.33	0	68.75	55
CP2 Post-Intervention	37.5	46.43	55.56	71.43	50	58.33	25	68.75	35
CP2 Follow-Up	31.25	78.57	72.22	96.4	47.5	55.56	5	31.25	80
CP3 Baseline	31.25	85.71	63.89	82.14	57.5	83.33	5	50	40
CP3 Post-Intervention	62.5	96.4	77.78	85.71	47.5	80.56	10	56.25	60
CP3 Follow-up	75	89.29	75	92.86	62.5	88.89	15	68.75	70
CP4 Baseline	43.75	82.14	72.22	89.29	62.5	55.56	5	53.13	35
CP4 Post-Intervention	31.25	75	50	92.86	52.5	61.11	0	50	30
CP4 Follow-up	31.25	85.7	63.89	100	62.5	63.88	0	81.25	50
CP5 Baseline	50	100	66.67	100	40	55.56	0	34.38	30
CP5 Post-Intervention	50	100	61.11	100	40	61.11	0	46.88	40
CP5 Follow-Up	37.5	100	75	100	40	63.88	0	46.88	40
CP6 Baseline	56.25	96.43	80.56	78.57	85	91.67	20	71.88	40

CP6 Post-Intervention	87.5	92.86	88.89	71.43	90	100	55	90.63	60
CP6 Follow-up	68.75	100	94.44	96.4	92.5	100	55	100	80
CP7 Baseline	43.75	89.3	97.22	100	32.5	50	5	34.38	65
CP7 Post-Intervention	56.25	96.4	91.67	82.14	35	61.11	5	46.88	55
CP7 Follow-up	25	100	97.22	82.14	32.5	50	5	25	55
CP8 Baseline	25	96.43	77.78	100	32.5	69.44	0	62.5	50
CP8 Post-Intervention	25	100	61.11	100	15	50	0	56.25	40
CP8 Follow-up	50	100	72.22	100	27.5	61.11	0	87.5	50
CP9 Baseline	56.25	92.86	83.33	100	37.5	52.78	0	50	50
CP9 Post-Intervention	56.25	82.14	83.33	100	42.5	66.67	0	68.75	30
CP9 Follow--up	37.5	89.29	69.44	100	37.5	58.33	0	56.25	20
CP10 Baseline	37.5	85.71	66.67	96.43	50	47.22	40	31.25	30
CP10 Post-Intervention	43.75	96.4	86.11	100	62.5	52.78	40	68.75	50
CP10 Follow-up	37.5	96.4	69.44	96.4	62.5	41.67	35	43.75	50
Mean (SD) Baseline	42.50 (10.94)	83.57 (17.10)	74.72 (11.45)	91.07 (9.26)	51.25 (16.34)	64.17 (15.41)	8.00 (12.74)	49.69 (14.62)	43.50 (11.32)
Mean (SD) Post-Intervention	50.63 (17.79)	87.13 (16.51)	71.67 (15.43)	88.93 (11.47)	48.50 (19.30)	66.39 (14.78)	15.00 (19.29)	57.81 (17.69)	40.50 (19.91)
Mean (SD) Three-Month Follow-up	44.38 (16.52)	90.35 (11.79)	77.50 (11.22)	94.99 (6.34)	52.75 (19.52)	65.55 (17.53)	13.00 (18.44)	59.38 (24.56)	57.00 (19.32)

Table H.31 Repeated measures ANOVA of SIS at baseline, post-intervention and follow-up

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
factor1	Sphericity Assumed	667.550	2	333.775	40.904	.000
	Greenhouse-Geisser	667.550	1.687	395.751	40.904	.000
	Huynh-Feldt	667.550	2.000	333.775	40.904	.000
	Lower-bound	667.550	1.000	667.550	40.904	.000
Error(factor1)	Sphericity Assumed	130.560	16	8.160		
	Greenhouse-Geisser	130.560	13.494	9.675		
	Huynh-Feldt	130.560	16.000	8.160		
	Lower-bound	130.560	8.000	16.320		

Table H.32 Post-hoc analysis: Paired Samples t-test of SIS scores at baseline and post-intervention and baseline and follow-up

		Paired Differences					Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference		
					Lower	Upper	
Pair 1	Baseline - POST	-8.99000	4.47606	1.49202	-12.43061	-5.54939	.000
Pair 2	Baseline – Follow-up	-11.61141	4.43095	1.47698	-15.01734	-8.20548	.000

Table H.33 Regression model of SIS post-intervention scores

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	24.182	18.150		1.332	.314
	Real_Sham	11.847	32.061	.354	.370	.747
	time_since_stroke	-3.446	7.311	-.106	-.471	.684
	Cortical_subcortical	-.061	4.941	-.001	-.012	.991
	PRE_SIS	.886	.150	1.067	5.919	.027
	SISxrs	-.211	.588	-.338	-.360	.754

a. Dependent Variable: POST_SIS

Table H.34 Regression model of SIS follow-up scores

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	27.145	8.320		3.263	.082
	Real_Sham	40.724	14.697	1.214	2.771	.109
	time_since_stroke	-7.318	3.351	-.225	-2.184	.161
	Cortical_subcortical	1.763	2.265	.036	.778	.518
	PRE_SIS	.968	.069	1.162	14.103	.005
	SISxrs	-.687	.270	-1.094	-2.548	.126

H.2.7 Hospital anxiety and depression scale (HAD)

The data of the individual participants of HAD are presented in the following tables.

Table H.35 HADS scores of the sub-acute and chronic group at baseline, post-intervention and three-month follow-up

Participant	Baseline (B)		Post-Intervention (P)		Follow-Up (F)		Change (P-B)		Change (F-B)	
	A*[1]	D*[2]	A	D	A	D	A	D	A	D
P03	8	9	8	9	7	6	0	0	-1	-3
P04	3	1	3	1	2	3	0	0	-1	+2
P05	11	12	11	12	7	8	0	0	-4	-4
P06	1	2	1	2	4	3	+1	0	+3	+1
P07	1	5	1	5	1	5	0	0	0	0
P08	1	1	1	1	1	1	0	0	0	0
P09	3	0	3	0	0	5	0	0	-3	+5
P10	8	3	8	3	6	2	0	0	-2	-1
P11	1	2	1	2	3	1	0	0	+2	-1
P12	4	5	4	5	5	9	0	0	+1	+4
CP1	3	8	5	11	4	10	+2	+3	-1	+2
CP2	12	10	8	10	11	11	-4	0	-1	+1
CP3	13	5	12	2	8	2	-1	-3	-5	-3
CP4	4	9	8	9	6	8	+4	0	+2	-1
CP5	3	8	5	9	2	9	+2	+1	-1	+1
CP6	2	6	3	4	0	0	+1	-2	-2	-6
CP7	0	4	1	5	2	3	+1	+1	+2	-1
CP8	3	2	6	2	5	1	+3	0	+2	-1
CP9	6	5	7	7	8	11	+1	+2	+2	+6
CP10	6	9	2	8	4	9	-4	-1	+2	0
Median (min,max) Sub-acute	3 (1,11)	2.5 (0,12)	3 (1,11)	2.5 (0,12)	3.5 (0,7)	4 (1,9)	0 (0,1)	0 (0,0)	-0.5 (-4,3)	0 (-4,
Median (min,max) Chronic	3.5 (0,13)	7 (2,10)	5.5 (1,2)	7.5 (2,11)	4.5 (0,11)	8.5 (0,11)	1 (-4,4)	0.0 (-3,3)	0.5 (-5,2)	-0. (-6,

H.3 Hand-Path ratio

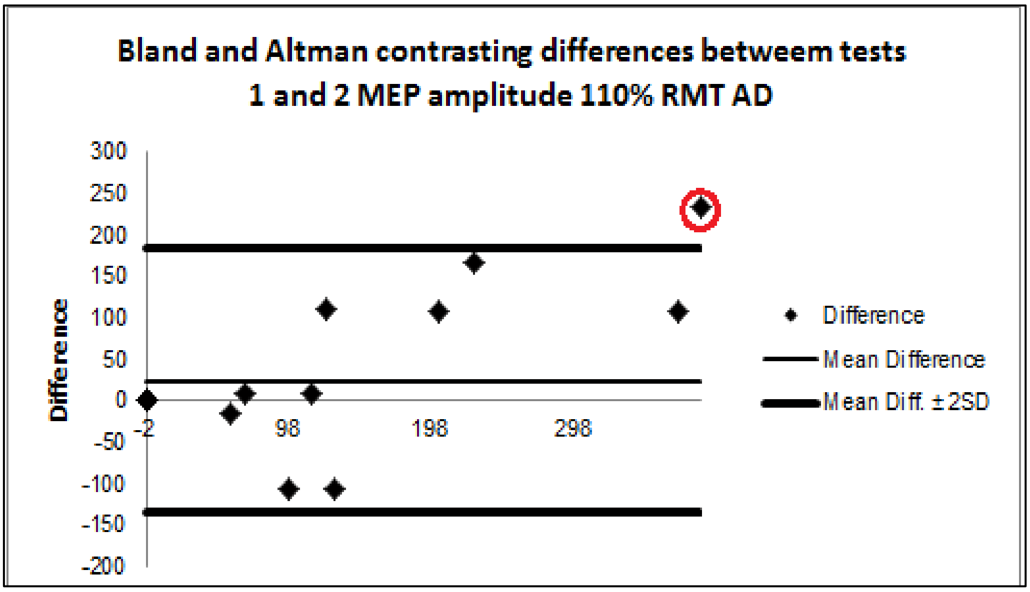
The individual data of the HPR is presented in the following table.

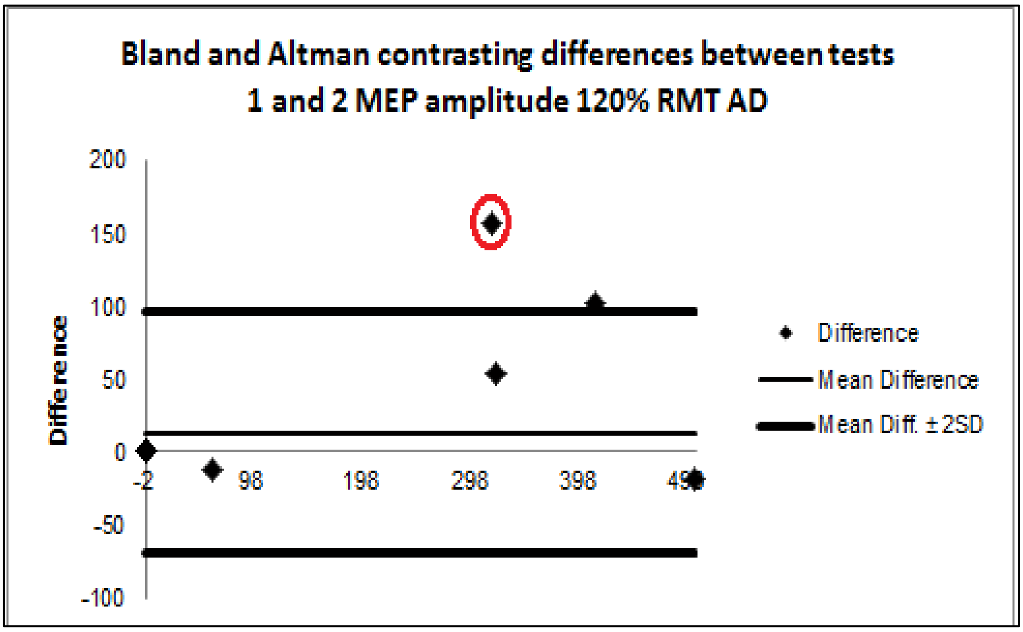
Table H.36 Individual data of the HPR during the 18 sessions

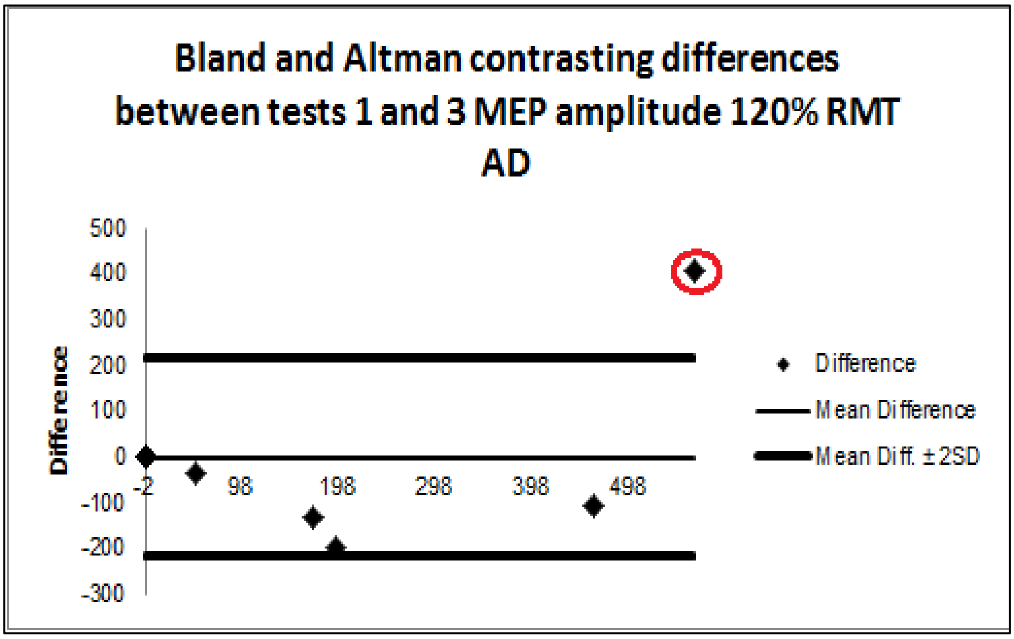
Session	P07	P08	P09	P10	P11	P12	Cp1	Cp2	Cp3	Cp4	Cp5	Cp6	Cp7	Cp8	Cp9	Cp10
1	1.965529	1.452348	1.91925	1.42648	2.093	1.347815	1.412778		1.752474	1.663533	1.787278	1.638227	1.306368	1.231842	1.113167	1.33055
2	1.453833	1.313439	1.793216	1.33562	1.78	1.259552	1.299857	2.17125	1.535684	1.351412	1.675231	1.352552	1.243222	1.253211	1.407923	1.244385
3	1.389053	1.308689	1.575	1.252	2.058375	1.369793	1.369857	1.962706	1.377684	1.4996	1.581417	1.558379	1.425722	1.257727	1.258929	1.239957
4	1.427964	1.290261	2.056571	1.29417	2.354938	1.263828	1.54575	2.1975	1.557412	1.401133	1.5383	1.480034	1.3147	1.366053	1.212842	1.164036
5	1.589714	1.253617	1.543571	1.26438	2.558667	1.406793	1.4184	2.130263	1.524842	1.359529	1.527706	2.10131	1.521036	1.234385	1.181647	1.124586
6	1.291621	1.231702	1.506674	1.17355	1.398	1.304655	1.3883	2.174353	1.623421	1.292647	1.333333	1.451862	1.435765	1.1978	1.430438	1.146931
7	1.284034	1.184936	1.499444	1.46141	2.041	1.366207	1.481625	2.200706	1.383842	1.325947	1.54004	1.623379	1.538	1.265556	1.182941	1.18828
8	1.464759	1.209064	1.523667	1.22197	1.450765	1.291621	1.303	1.955632	1.26	1.372824	1.66044	1.482862	1.475607	1.3646	1.199353	1.168321
9	1.35969	1.18366	1.526837	1.23855	1.475636	1.256483	1.625222	2.840176	1.373632	1.555294	1.635462	1.51169	1.63184	1.237842	1.140684	1.154593
10	1.362414	1.183681	1.430489	1.2079	1.340529	1.358655	1.476636	2.056474	1.454368	1.271737	1.79352	1.508345	1.332391	1.243368	1.200211	1.24369
11	1.327621	1.189872	1.555787	1.25803	2.4266	1.246586	1.360538	1.830158	1.307474	1.380133	1.761043	1.510458	1.518345	1.236632	1.276471	1.26663
12	1.362828	1.165511	1.629395	1.25093	1.855	1.273103	1.424143	2.290211	1.466368	1.349867	1.41644	1.82763	1.575655	1.198579	1.148211	1.228069
13	1.33469	1.157404	1.534837	1.16534	1.3096	1.338862	1.316	2.222211	1.254632	1.403737	1.374138	1.551	1.504448	1.129158	1.189947	1.240192
14	1.376138	1.155426	1.482787	1.19459	1.205474	1.201345	1.499727	2.083789	1.300263	1.326647	1.64144	1.458897	1.536414	1.164263	1.142895	1.213964
15	1.273897	1.159234	1.383156	1.20245	1.255059	1.194172	1.780333	1.875947	1.251789	1.279412	1.397724	1.539759	1.410586	1.151421	1.116263	1.196862
16	1.415793	1.117574	1.477178	1.17859	1.332706	1.186276	1.399353	2.664632	1.245368	1.323	1.618607	1.554586	1.500448	1.168895	1.178895	1.174222
17	1.260414	1.116915	1.495628	1.20355	1.272737	1.198379	1.5444	2.461368	1.414053	1.424	1.648444	1.40263	1.495069	1.201059	1.145947	1.234296
18	1.300862	1.138255	1.344889	1.30031	1.440947	1.160552	1.417824	2.63	1.189	1.275368	1.31269	1.463172	1.500931	1.168882	1.181947	1.232586
Mean	1.40227	1.211755	1.571021	1.25721	1.702724	1.279149	1.447986	2.220434	1.404017	1.380879	1.56907	1.556487	1.459253	1.226182	1.206039	1.210675

H.4 Reliability Study- Extra Bland and Altman Plots

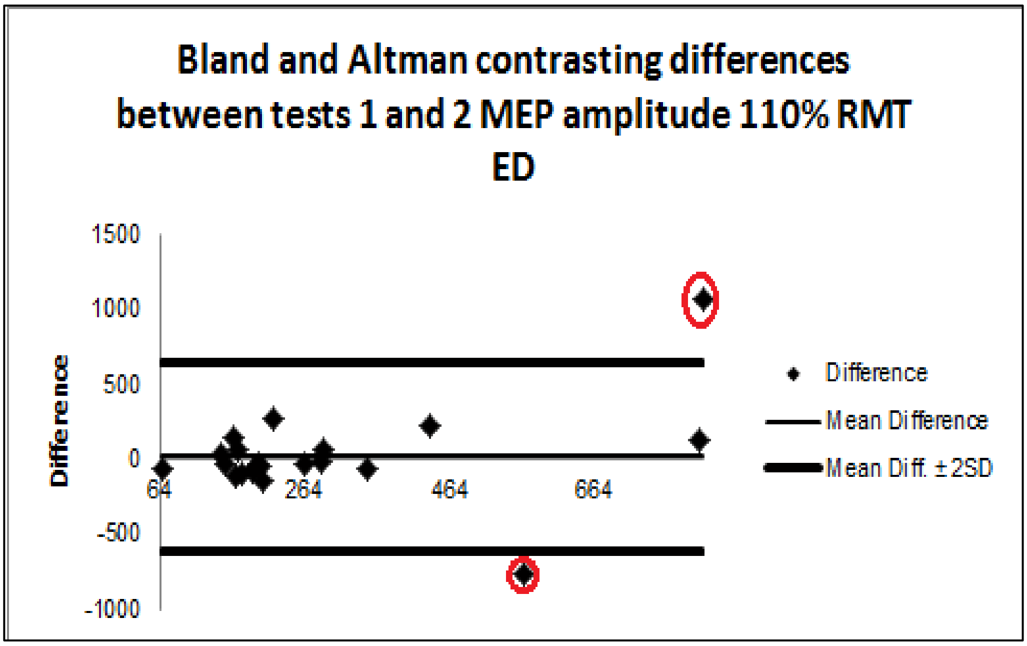
Anterior Deltoid muscle (AD)

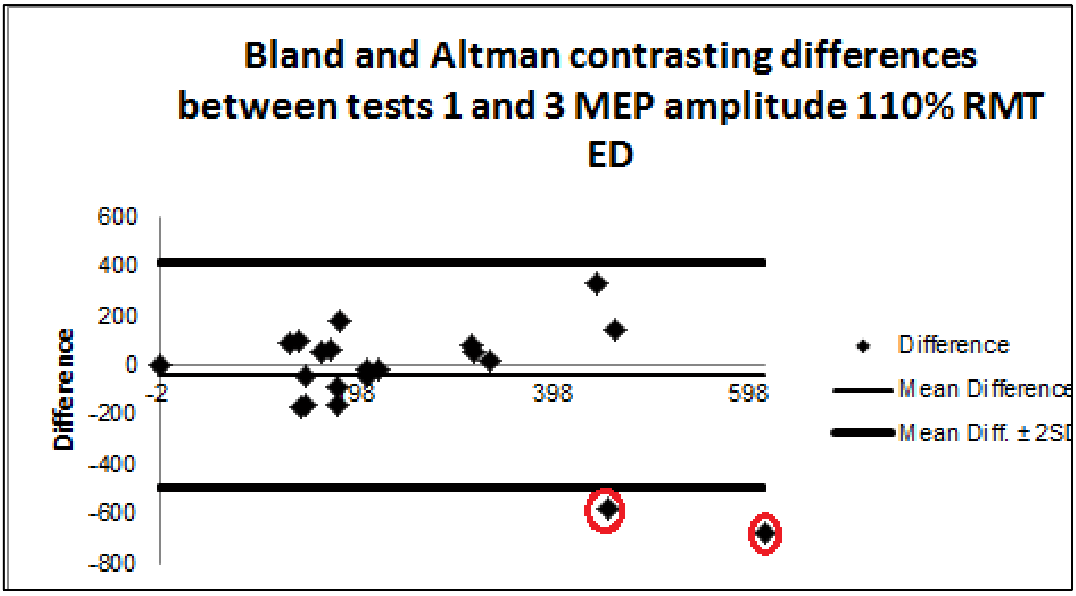




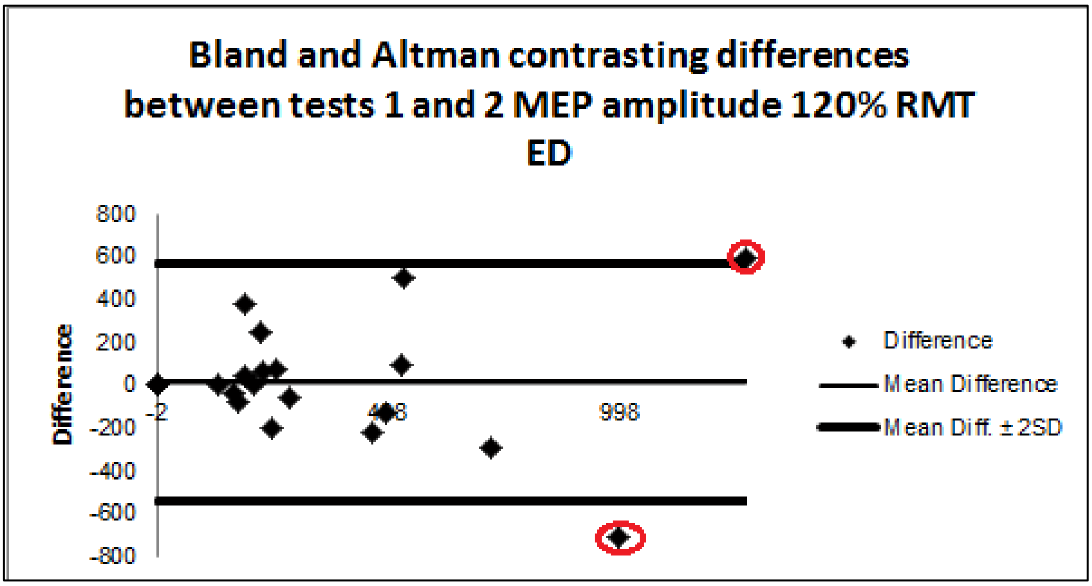


Extensor Digitorum muscle (ED)

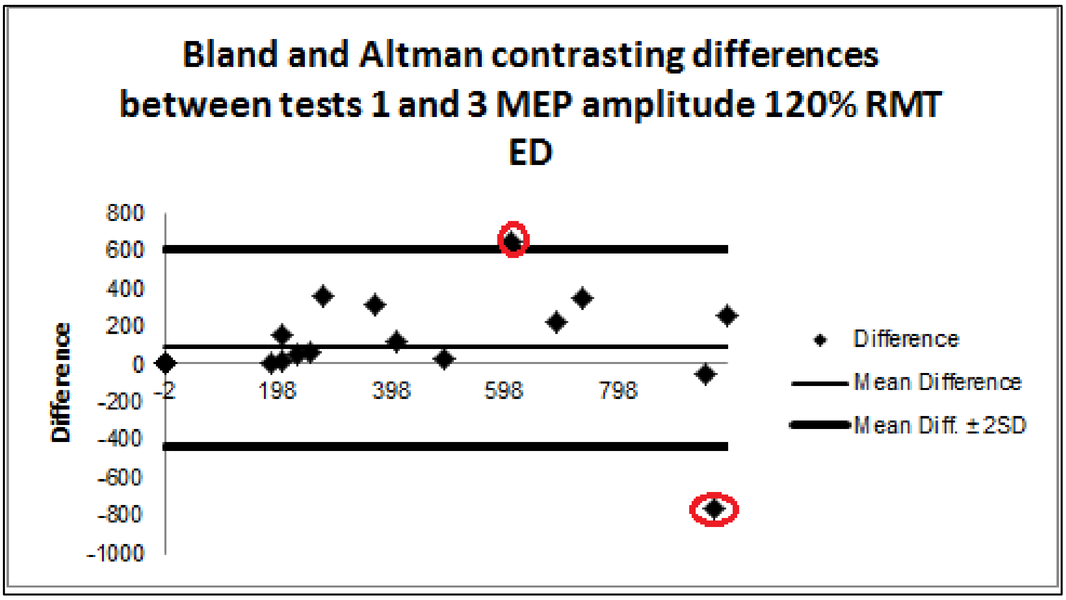




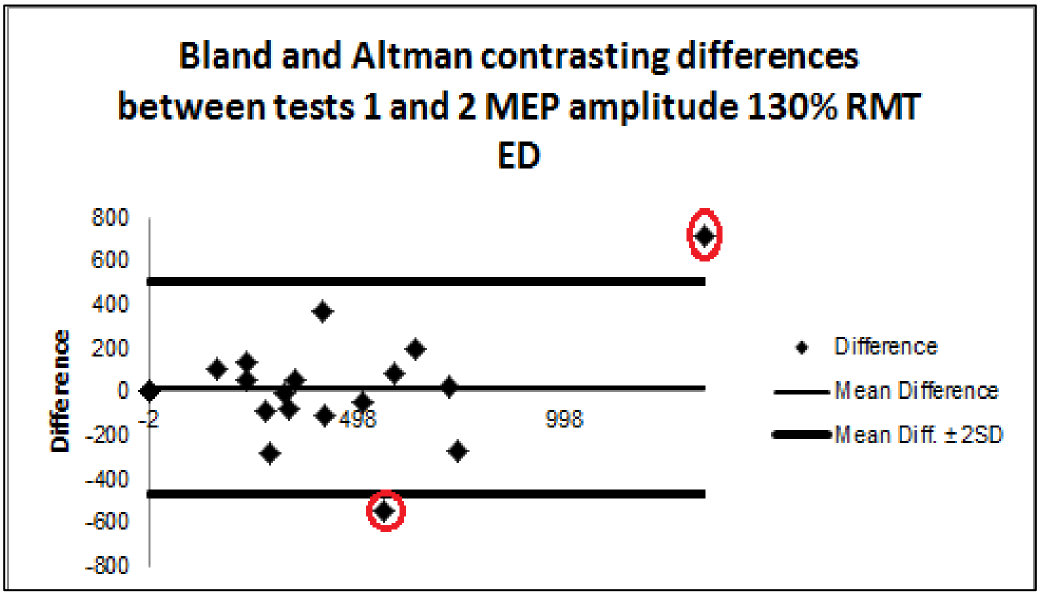
Bland and Altman contrasting differences between tests 1 and 3 MEP amplitude 110% RMT ED
600
400
200
0
-200
-400
-600
-800
Difference
-2
398
598
Difference
Mean Difference
Mean Diff. ±2SD



Bland and Altman contrasting differences between tests 1 and 2 MEP amplitude 120% RMT ED
800
600
400
200
0
-200
-400
-600
-800
Difference
-2
998
Difference
Mean Difference
Mean Diff. ±2SD



Bland and Altman contrasting differences between tests 1 and 3 MEP amplitude 120% RMT ED
800
600
400
200
0
-200
-400
-600
-800
-1000
Difference
-2
198
398
598
798
Difference
Mean Difference
Mean Diff. ±2SD


Bland and Altman contrasting differences between tests 1 and 2 MEP amplitude 130% RMT ED
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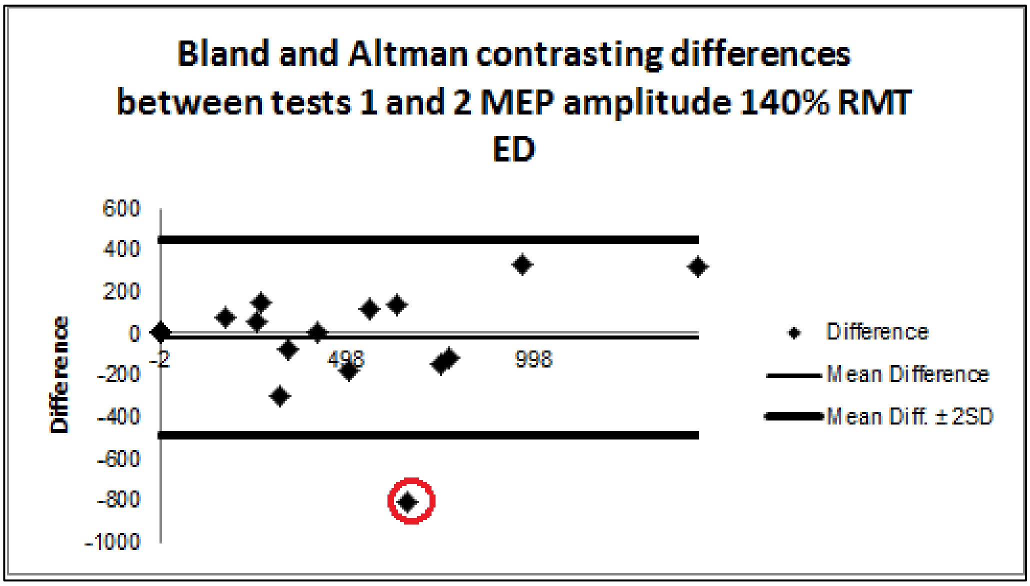
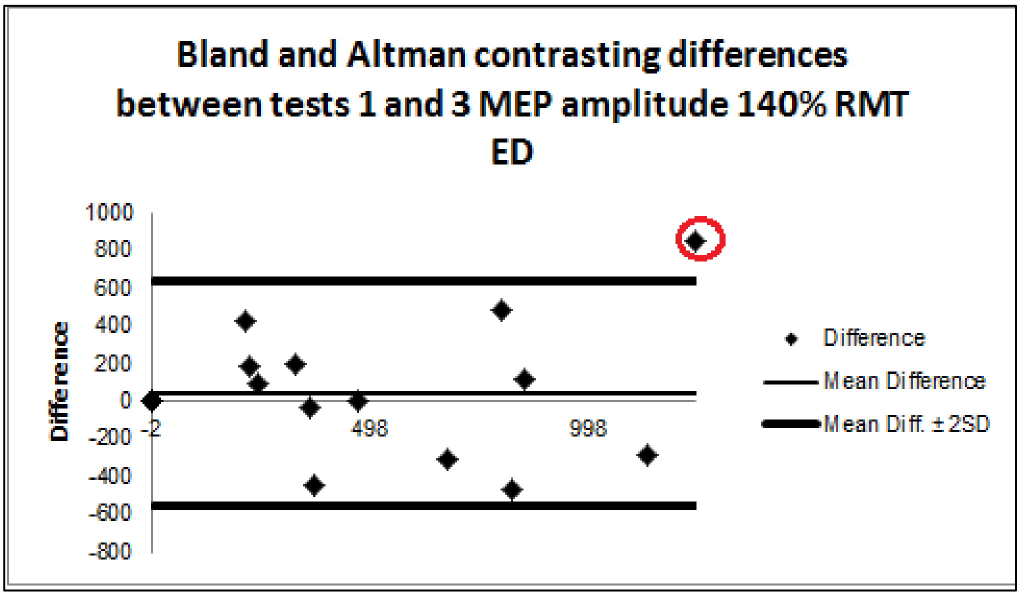
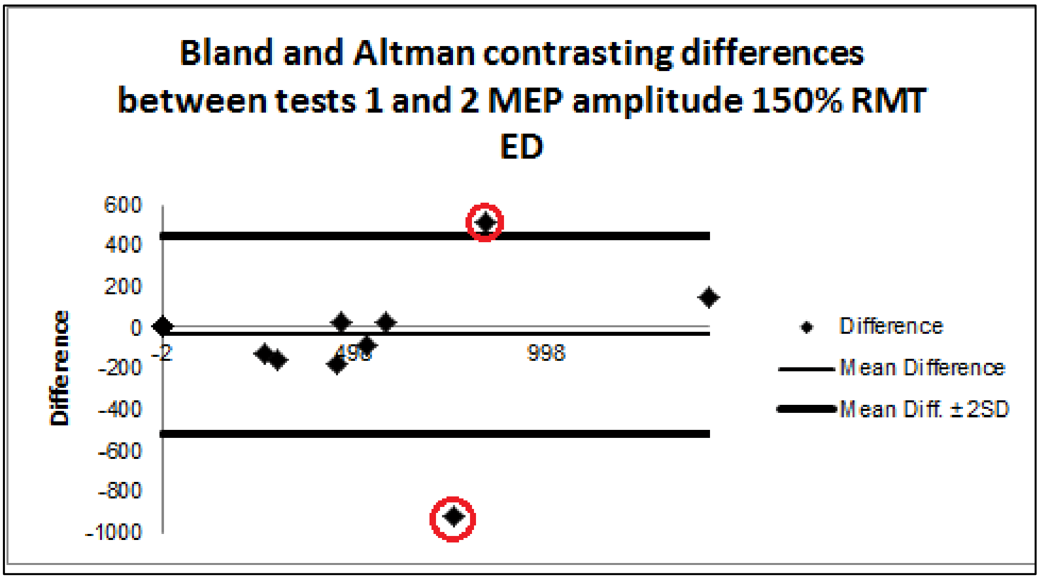
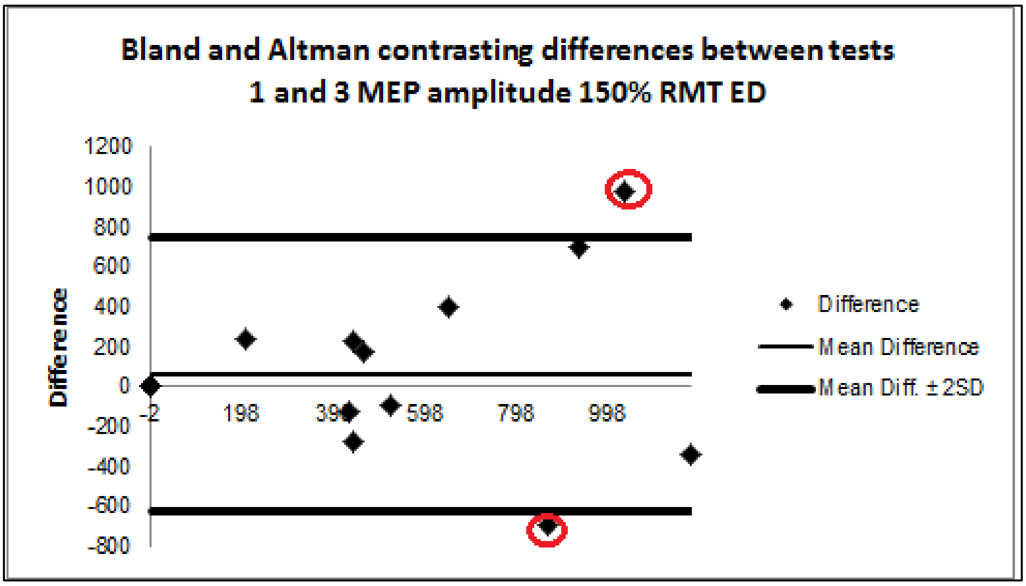
600
400
200
0
-200
-400
-600
-800
Difference
-2
498
998
Difference
Mean Difference
Mean Diff. ±2SD


Bland and Altman contrasting differences between tests 1 and 2 MEP amplitude 140% RMT ED
600
400
200
0
-200
-400
-600
-800
-1000
Difference
-2
498
998
Difference
Mean Difference
Mean Diff. ±2SD


Bland and Altman contrasting differences between tests 1 and 3 MEP amplitude 140% RMT ED
1000
800
600
400
200
0
-200
-400
-600
-800
Difference
-2
498
998
Difference
Mean Difference
Mean Diff. ±2SD



Bland and Altman contrasting differences between tests 1 and 2 MEP amplitude 150% RMT ED
600
400
200
0
-200
-400
-600
-800
-1000
-2
498
998
Difference
Difference
Mean Difference
Mean Diff. ±2SD



Bland and Altman contrasting differences between tests 1 and 3 MEP amplitude 150% RMT ED
1200
1000
800
600
400
200
0
-200
-400
-600
-800
-2
198
398
598
798
998
Difference
Difference
Mean Difference
Mean Diff. ±2SD

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Glossary

Bland and Altman plot presents the level of agreement between two variables

Confidence interval gives an estimated range of values

Diffusion weighted imaging is a form of magnetic resonance imaging based upon the diffusion of water molecules within a voxel.

Fixed-effect model is based on the mathematical assumption that a single common (or 'fixed') effect underlies every study in the meta-analysis

Functional magnetic resonance imaging is a technique for measuring brain activity. It works by detecting the changes in blood oxygenation and flow that occur in response to neural activity

Gamma-Aminobutyric acid is an inhibitory neurotransmitter in the central nervous system

Glutamate is a non-essential amino acid and neurotransmitter which is important for long-term potentiation

Hand path ratio is a kinematic measurement of distance between the cursor and the target which is calculated the length of the pathway divided by the straight line distance

Incidence is a frequency of a disease

International Classification of Functioning, Disability and Health (ICF) model displays a framework for assessing the consequences of a health condition such as stroke in terms of function and disability. This framework focusses on the pathology, impairment, activity (limitations) and participation (restrictions)

Long-term potentiation is based on the long-lasting increase in synaptic efficacy after tetanic stimulation of the presynaptic neuron. The long-lasting change is a result of presynaptic neurotransmitter release and increased postsynaptic receptor expression, the N-methyl-D-aspartic acid glutamate receptor

Magnetic resonance spectroscopy is a non-invasive diagnostic test for measuring biochemical changes in the brain

Meta-analysis adds power to the decision making from a systematic review

Minimum Detectable Change is the minimum change in resting motor threshold or MEP amplitude over a given period of time required to be considered statistically significant

Motor cortex is the region of the cerebral cortex which involves planning, control, and execution of voluntary movements. It consists of the premotor and primary motor cortex and supplementary motor area

Motor evoked potential is an electrical potential recorded from a muscle as a result of cortical stimulation

Neuroplasticity is the term for the ability of the brain and the central nervous system to obtain new information and adjust to environmental change by changing its neural connectivity and function

N-methyl-D-aspartic acid receptor is a ligand-gated calcium channel. The receptor is a binding site on the extracellular surface for glutamate (a neurotransmitter) that directs the opening of the channel

Neglect is the inability to orient towards and attend to stimuli, including body parts, on the side of the body affected by the stroke

Nonparametric statistics refers to statistics that do not assume the data or population have any characteristic structure or parameters

Null hypothesis refers to when there is no relationship between two measured phenomena

Parametric statistics is a branch of statistics which assumes that the data has come from a type of probability distribution and makes inferences about the parameters of the distribution

Prevalence is how common the condition is in the current population

Randomised controlled trial is a type of scientific experiment used to test the efficacy and effectiveness of an intervention within a patient population

Random effects model makes the assumption that individual studies are estimating different treatment effects in the meta-analysis

Regression analysis is a statistical process for estimating the relationships among variables

Reliability of a measure refers to the extent the measurement is free from error and also consistent

Repeated measures Analysis of Variance is a commonly used statistical approach for repeated measure design to assess the change over time within and between subjects

Resting motor threshold is the minimal intensity to result in an motor evoked potential at an amplitude of 50 microvolts

Robot is defined as a ‘machine’ which is designed to function in place of a living agent and carries out a variety of tasks automatically

Transcranial direct current stimulation is a form of neurostimulation which uses constant, low current delivered directly to the brain area of interest via small electrodes, via anodal, cathodal or bihemispheric applications

Transcranial Magnetic Stimulation is a non-invasive method to cause depolarization or hyperpolarization in the neurons of the brain by placing a magnetic coil on the individual’s head

Skill is the capability of carrying out a task such as lifting a cup from the table to the mouth, with efficiency and fluency

Spasticity is disordered sensori-motor control, resulting from an upper motor neurone lesion, presenting as intermittent or sustained involuntary activation of muscles

Standard deviation is a measure of the dispersion of a set of data from its mean

Standard error of mean is a measure of the precision of a test instrument. It is calculated on the basis of sample data using the sample SD and the sample reliability coefficient

Standardised mean difference is used as a summary statistic in meta-analysis when the studies all assess the same outcome but measure it in a variety of ways

Statistical significance is the probability that an effect is not due to just chance alone

Stroke can be defined as: “rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin”

Stroke rehabilitation is an active process beginning during the acute setting, which can progress for those with residual impairments to a systematic programme of rehabilitation services, and continuing after the individual returns to the community

Systematic review presents an overview of primary studies using an explicit, transparent and reproducible method. It is an efficient scientific technique of integrating scientific information and evaluating decision-making

Thematic analysis is a qualitative data analysis approach which involves identifying, analysing, and reporting patterns (themes) within data

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