Strength for Task Training

A novel intervention

to improve locomotor ability

following stroke

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2014

A thesis submitted to

Auckland University of Technology

in fulfilment for the degree of

Doctor of Philosophy (PhD)

School of Rehabilitation and Occupation Studies

ABSTRACT

Many people with stroke have ongoing difficulty with locomotor abilities to the extent that it limits their participation in meaningful community life. Deficits in locomotor ability are strongly related to muscle weakness following stroke. Whilst the majority of physical therapy time is spent on the rehabilitation of locomotor abilities, the most effective rehabilitation method has yet to be determined. The need to develop efficacious rehabilitation strategies to address locomotor disability following stroke is paramount. Therefore, the primary aim of this thesis was the development of a novel intervention to improve locomotor ability in people following stroke.

Systematic reviews of the evidence base were undertaken, evaluating two rehabilitation interventions; strength training and task-specific training. It was identified that strength training results in considerable increases in muscle strength. Yet despite the strong relationship between strength and locomotor ability, gains in strength following strength training translate poorly into improvements in locomotor ability. In considering task-specific training, the findings indicate that it improves locomotor ability; however gains are modest at best. These reviews suggested that the limited outcomes seen may relate to a failure to train people with stroke at sufficient intensity and dose, and with specificity to locomotor disability. A narrative review of the neuroscience literature in relation to the neural control of walking and neural plasticity elucidated a role for strength training to act as a priming intervention prior to task-specific training in people with stroke. Collectively this information informed the development of a novel intervention to improve locomotor ability following stroke; Strength for Task Training (STT). The key features of STT are that strength training is utilised to systematically prime the central nervous system prior to task-specific training and that strength training and task-specific training are conducted in an evidence based manner to maximise gains in locomotor ability.

As part of the development of the STT intervention and preparation for evaluation, the selection of valid and reliable outcome measures was considered. The identification of suitable measures of the neural plasticity underlying recovery proved challenging. Therefore, a feasibility assessment of potential outcome measures was undertaken, identifying two possibilities; Transcranial magnetic stimulation (TMS) derived measures of corticomotor excitability and serum measurement of the neurotrophin, brain derived neurotropic factor (BDNF). In order to establish the test-retest reliability of these measures, two repeated measures studies were undertaken. These studies established the

excellent test-retest reliability of TMS-derived measures when taken during treadmill walking. However, BDNF proved a less reliable measure.

The final study of this thesis was a mixed methods pilot study which evaluated the feasibility of the research protocol for testing the STT intervention in a randomized controlled trial and the acceptability of the STT intervention to people with stroke and physiotherapists. This pilot study established the feasibility of the sampling and recruitment strategy, the integrity of the trial protocol and the feasibility, acceptability and safety of the STT intervention. The rigorous implementation of this mixed methods pilot study enabled refinement of both the study protocol and intervention, safeguarding the success of future evaluation in a large randomised controlled trial and translation of this novel intervention into clinical practice.

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ABBREVIATIONS

1-RM	1-Repetition maximum
30sCST	30 second chair stand test
6MWT	Six minute walk test
ABC	Activities-specific balance and confidence scale
AMT	Active motor threshold
ANOVA	Analysis of variance
BDNF	Brain derived neurotrophic factor
BW	Body weight
CI	Confidence interval
CNS	Central nervous system
CV	Coefficient of variation
CWS	Comfortable walking speed
EMG	Electromyography
FWS	Fast walking speed
HR	Heart rate
HRQoL	Health related quality of life
ICC	Intra-class correlation coefficient
ICF	International classification of functioning, disability and health
MAS	Motor assessment scale
MEP	Motor evoked potential
MMSE	Mini-mental state exam
MoCA	Montreal cognitive Assessment
MRC	Medical research council
MVC	Maximal voluntary contraction
NZ	New Zealand
PRST	Progressive resisted strength training
rANOVA	Repeated measures ANOVA
RM	Repetition maximum
RMS	Root mean square
RPE	Rating of perceived exertion
SD	Standard deviation
SEM	Standard error of the measure
SIPSO	Subjective index of physical and social outcome

SIS	Stroke impact scale
STT	Strength for task training
TE	Typical error
TMS	Transcranial magnetic stimulation
TST	Task-specific training
TUAG	Timed up and go

ATTESTATION OF AUTHORSHIP

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

ACKNOWLEDGEMENTS

INTRODUCTION

Stroke is a central nervous system (CNS) pathology which occurs as a result of compromise to the circulation of the brain, leading to permanent tissue damage through anoxia and ischemia [1]. Injury to the cortical and/or sub cortical structures of the brain may affect the sensory, perceptual, cognitive and motor systems. Whilst there may be considerable spontaneous recovery following stroke, ongoing deficits in impairment, function, participation and health related quality of life (HRQoL) after stroke are common [2]. Globally stroke is a leading cause of disability for individuals, and represents a significant burden to the person, their family, society and healthcare systems [3]. In New Zealand (NZ) there are approximately 45 000 stroke survivors, and despite continued efforts to reduce the risk of stroke, this number is predicted to continue to rise due to improved survival and aging of the population [4, 5].

As many as 92% of people with stroke discharged from inpatient rehabilitation services have ongoing difficulty with locomotor abilities, to the extent that it limits their participation in meaningful community life [6]. The need to develop efficacious rehabilitation strategies to address locomotor disability following stroke is paramount. Locomotor abilities are high valued by people following stroke [7, 8], and locomotor disability is associated with increased dependency, limited social participation, reduced HRQoL, and increased health burden [9].

Whilst the majority of physical therapy time is spent on the rehabilitation of locomotor abilities [10-13], the most effective method of rehabilitating locomotor ability has yet to be determined [14]. However, rehabilitation research addressing locomotor disability has recently been subjected to a number of criticisms including a failure to;

- ground the development of rehabilitation interventions in sound theory and scientific evidence [15-17]
- facilitate patients engagement with the intervention development process [15]
- define the essential elements of the intervention and its mechanism of action[18]
- adequately describe intervention [19, 20]
- strategically evaluate interventions in a step wise manner [21]
- select outcomes which reliably measure and describe the intervention effect [21]
- compare new interventions to relevant parallel treatment interventions [21]

In light of these criticisms this doctoral thesis sought to undertake a rigorous process in the development and feasibility and pilot testing of a complex intervention to improve locomotor ability in people with stroke. Locomotor rehabilitation was considered a complex intervention because rehabilitation interventions have a number of interacting components, they require a high level of flexibility and tailoring in implementation, and the intervention effects are likely to be variable and extend across a broad range of outcomes [22]. Reference was made to the Medical Research Councils (MRC) recommendations for the development of complex interventions [22]. The MRC describes an iterative process of intervention development and evaluation which includes four inter-related phases; Development, Feasibility and Piloting, Evaluation and Implementation. Refer to Figure 1-1 for a pictorial representation of this process.

Feasibility and Piloting
Testing procedures
Estimating recruitment and retention
Determining sample size

Development
Identifying the evidence base
Identifying and developing theory
Modelling process and outcomes

Evaluation
Addressing effectiveness
Understanding change process
Assessing cost effectiveness

Implementation
Dissemination
Surveillance and monitoring
Long term follow-up

[22] Pg. 980

Figure 1-1 Medical Research Councils- Key Elements in the Development and Evaluation Process for Complex Interventions

This thesis addresses the Development and Feasibility and Piloting of the intervention Strength for Task Training (STT); and is divided into three sections:

Section 1.   Intervention Development

Section 2.   Measurement of Neural Plasticity in Response to Locomotor Rehabilitation

Section 3.   Strength for Task Training: A Pilot Study

The first section; Intervention Development, describes the preclinical or theoretical phase of the development of a complex intervention to improve locomotor ability following stroke. This section incorporates four chapters:

Chapter 1. Background

Chapter 2. Systematic Review of the Evidence

Chapter 3. Scientific Underpinnings

Chapter 4. Defining the Intervention

Chapter 1 provides context by describing the scope of locomotor disability following stroke, illustrating the parameters of recovery and determinants of locomotor ability in people with stroke. This chapter specifically focuses on the importance of muscle weakness as a key impairment contributing to locomotor disability. Chapter 2 addresses the current evidence for improvements in locomotor ability in response to two rehabilitation interventions; strength training and task-specific training, by undertaking two systematic reviews. These systematic reviews ask the questions; *Are these interventions effective at improving locomotor ability in people with stroke?* and *What are the training parameters utilised in the research when applying these interventions in people with stroke?* The intent of these systematic reviews was to better understand the relationship between the training parameters applied, how they met current recommendations and the extent to which they resulted in gains in locomotor function. Chapter 3 includes a narrative review of recent advances in the understanding of the neural control of walking and neural plasticity in response to strength and task –specific training. By exploring the neuroscience literature it was expected to ground the development of the intervention in the scientific evidence. Following review of the rehabilitation research evidence and neuroscience literature the concept for a novel intervention to improve locomotor ability after stroke was developed.

T*he premise of STT was that a systematic and structured combination of unilateral progressive resisted strength training (PRST), to improve strength and prime the central nervous system, with task-specific training (TST) to induce permanent neuroplastic changes, would result in greater gains in locomotor ability than either intervention on their own.*

The defining features of the STT intervention were that; strength training was utilised to systematically prime the central nervous system prior to task-specific training and that strength training and task-specific training were conducted in an evidence based manner to maximise gains in locomotor ability, with reference to the relevance, specificity, intensity, progression and dose of the intervention. Chapter 4 further describes the process of defining the key features of the intervention and consultation with key stakeholders which resulted in a number of important refinements to the intervention prior to piloting.

As part of the process of developing the intervention and preparing it for evaluation in a pilot study the selection of valid and reliable outcome measures was considered. The intention was to select outcome measures across the spectrum of the International Classification of Functioning, Disability and Health to provide a broad view of the intervention effects [15, 23]. This was considered particularly important for the pilot trial where the purpose of the research includes identifying the breadth of effects across a range of domains [22]. While measures of impairment, locomotor ability and participation in stroke, with good psychometric properties, were identified [24, 25], the identification of suitable measures of the biological processes underlying recovery proved more challenging. Therefore the section; Measurement of Neural Plasticity in Response to Locomotor Rehabilitation addresses this issue. This section comprises three chapters:

Chapter 5. Measurement Selection
Chapter 6. Test-retest Reliability of BDNF Measures
Chapter 7. Test-retest Reliability of TMS measure

Chapter 5 describes the feasibility assessment undertaken to identify appropriate outcome measures of neural plasticity, whilst Chapter 6 and Chapter 7 describe two repeated measures studies investigating the test-retest reliability of two potential measures of neural plasticity; Brain Derived Neurotropic Factor (BDNF) and Transcranial Magnetic Stimulation (TMS). The establishment of measurement reliability and the importance of using this reliability data to determine sample and effect sizes in research trials are paramount to good scientific practice. The measurement of serum BDNF as a biomarker of neural plasticity was a relatively novel field of scientific enquiry and this

study is the first, to the authors' knowledge, to explore BDNF levels in people with stroke and to consider the reliability of the measure in both healthy people and people with stroke. Chapter 7 addressed the reliability of TMS in healthy people and people with stroke, seeking to establish a more reliable method for the measurement of corticomotor excitability in the lower limb muscles in people with stroke than had been previously identified.

The final section of this thesis is entitled; Strength for Task Training: A Pilot Study. The first part of this chapter provides context to the method of scientific enquiry and emphasises the strengths of pilot studies and mixed methods approaches in informing the development and evaluation of complex interventions. Then a description of the pilot testing of the intervention is undertaken. The aim of this pilot study was to evaluate feasibility of the research protocol for testing the STT intervention in a randomized controlled trial. Therefore, the specific aims of this pilot study were to; (1) Establish the feasibility of the sampling and recruitment strategy, (2) Establish the integrity of the trial protocol, (3) Establish the feasibility, acceptability and safety of the STT intervention, (4) Establish the magnitude of the difference and variance estimates of the outcome measures. The rigorous implementation of this mixed methods pilot study enabled refinement to both the study protocol and intervention, safeguarding the success of future evaluation in a large randomised controlled trial and translation of this novel intervention into clinical practice.

SECTION ONE:

INTERVENTION DEVELOPMENT

Chapter 1   Background

1.1   Prologue

The Intervention Development section of this thesis undertakes a review of the evidence base and theoretical literature which underpinned the conception of the STT intervention. Chapter 1 provides background to the problem by describing the recovery and the determinants of locomotor ability following stroke.

1.2   Introduction

Locomotion refers to the ability to move from place to place [26]. When discussing locomotion following stroke most authors use the term locomotor ability interchangeably with walking. However, locomotion may also entail skills such as moving on and off surfaces (bed, chair, floor) and stair climbing. This is particularly relevant when considering locomotion in the community which may also include additional demands (i.e. negotiating obstacles and terrains), mobilising under different environmental conditions (i.e. in crowds, during low lighting and inclimate weather), for extended distances, at variable speeds and whilst carrying loads and undertaking secondary tasks [9, 27, 28]. Limited recovery of locomotor abilities in people with stroke is associated with dependency, limited social participation, reduced quality of life, and increased health burden to the individual, family and society [29].

1.3   Recovery of Locomotor Ability after Stroke

Immediately following a stroke as few as 27% of people are able to walk independently, yet by the end of inpatient rehabilitation approximately 70% gain the ability to walk 46 metres [30]. However, these findings reflect a very gross measure of indoor walking ability and do not highlight the spectrum of deficits in locomotor ability a person with stroke may experience. Nor do they reflect the need for walking aids and considerable limitations in walking speed and endurance which are common after stroke [31]. Walking speed has been related to community locomotion; with people who walk less than 0.4m/s being classified as household ambulators, those who walk between 0.4-0.8m/s as limited community ambulators and those who walk more than 0.8m/s as full community

ambulators [32]. One study of 185 patients in a stroke rehabilitation unit reported a median walking speed of 0.45 m/s at seven days post-stroke and 0.55m/s at discharge from rehabilitation [31]. Large scale studies describing locomotor deficits in people with chronic stroke are scant however, intervention studies report mean walking speeds of between 0.6m/s and 0.75m/s prior to intervention in community dwelling individuals with chronic stroke, dependent on the study inclusion criteria [33-36]. Regardless, residual deficits in walking speed are marked when compared to healthy older adults whose preferred walking speed is usually in excess of 1.2m/s [37]. Recovery of walking speed appears to be greatest in the first six weeks after stroke and then the rate of recovery tends to slow; however gains in walking speed in response to interventions have been reported in people who are a very long time post-stroke [38]. Deficits in walking endurance have also been reported in the acute and chronic phase following stroke [39, 40]. Whilst related to locomotor ability; walking velocity and endurance may not fully reflect the locomotor challenges an individual may face when in the community [28, 29, 41]. Importantly, as many as 92% of people who have a stroke who are discharged from inpatient rehabilitation have ongoing difficulty with locomotor abilities, to the extent that it limits their participation in meaningful community life [6, 7, 29].

1.4   Determinants of Locomotor Ability after Stroke

Studies investigating the impairments which cause locomotor disability following stroke highlight that locomotor disability is related to the extent of motor impairment, particularly muscle strength and power [42-45], cardiovascular fitness [44, 46], balance [44, 47, 48], self-efficacy and mood [49]; with the relative contribution of each impairment seemingly related to the time since stroke and the severity of disability.

Deficits in muscle strength are one of the primary impairments which limit locomotor function following stroke [2, 50-52]. Different locomotor abilities place different demands on different muscles; for instance the strength of the plantarflexor and hip flexor muscles strongly correlates with walking speed and endurance in people after stroke [43, 45, 50], whilst the strength of the hip extensors, flexors and knee extensors are important for successful performance of stair climbing [53]. This highlights the pivotal role of muscle strength to locomotor ability following stroke.

1.5   Muscle Weakness following Stroke

Muscle strength is defined as the ability to generate force against a load and is assessed as the maximum load that can be moved or the maximum torque that can be generated

during a movement. Deficits in muscle strength are common in both the affected and unaffected side following stroke [54]. Two other aspects of muscle strength which are affected after stroke are; 1) muscle endurance, the ability to generate torque against a load for an extended period of time and 2) muscle power, the ability to generate torque against a load at speed [42, 55].

Research in people with stroke reveals that there are neural, as well as muscle structure and function changes following stroke which may to contribute to deficits in muscle strength. It is assumed that these changes reflect both primary impairments, directly caused by the stroke, and secondary changes due to immobility and physical inactivity.

The impact of neural changes following stroke on muscle strength is grossly quantified using voluntary activation [56]. Voluntary activation refers to the extent to which the central nervous system is driving the muscle at the time of a muscle contraction. During a maximal voluntary contraction, voluntary activation in people without pathology is between 90 and 100% of the total capacity of the muscle. A number of studies in people with stroke have identified marked deficits in voluntary activation, with voluntary activation of between 60-83% on the affected side and 60-95% on the unaffected side [57-60]. Deficits in voluntary activation are likely caused by neural changes in the excitability of the cortical, subcortical and spinal contributions to muscle activation [61, 62], along with alterations in motor unit recruitment [63, 64]. These changes are presumed to reflect the neuronal damage caused by the brain lesion and secondary disuse [61, 62, 65]. Alterations in muscle structure and function following stroke are evidenced by research demonstrating; muscle atrophy, fibre type alterations and muscle structure changes after stroke [66-68].

1.6 Summary

In summary, stroke can result in considerable locomotor disability which may limit an individual's participation in the community. Deficits in locomotor ability are strongly related to muscle weakness following stroke. Muscle weakness is likely caused by primary impairments in neural activation and secondary neural and muscular impairments.

Chapter 2   Systematic Reviews of the Evidence Base

2.1 Prologue

Whilst the majority of physical therapy time is spent on the rehabilitation of locomotor abilities [10-13], the most effective method of rehabilitating locomotor ability has yet to be determined [14]. However, it is difficult to evaluate the effect of individual physiotherapy approaches due to a failure of the research literature to adequately describe them [69-71]. This section focuses on the research evidence to support, and the described training parameters of, two physiotherapy approaches to locomotor rehabilitation; strength training and task-specific training.

2.2 Introduction

Whilst a number of recent systematic reviews have been undertaken in relation to strength training [72, 73] and task-specific training [74, 75], these reviews do not explicitly consider the training parameters utilised during the interventions. Therefore to better understand the evidence base and the training parameters utilised in applying strength training and task-specific training in people with stroke, two systematic reviews guided by the methodology described by the PRISMA statement [76] were undertaken. Each review asked two questions;

> *Is the specified intervention effective at improving locomotor ability in people with stroke?*

> *What are the training parameters utilised in the research when applying the specified intervention in people with stroke?*

Effectiveness was considered with respect to statistically significant within and between group differences in outcomes of interest..

2.3 Methods

2.3.1 Eligibility criteria

Evidence was selected based on predetermined criteria. To be considered suitable for review a trial had to;

- be randomised as defined by the CONSORT group [77]
- include participants who were adults who had a stroke and experienced locomotor disability
- investigate an intervention which met the defined description of the interventions as outlined in section 2.4 and 2.5 respectively
- include a control intervention which was dissimilar to the intervention under investigation; and either a placebo intervention not expected to result in locomotor gains or an intervention considered usual care or standard physiotherapy practice
- measure outcomes of locomotor ability including; aspects of walking (speed, endurance, dual tasking, negotiating obstacles and terrains), sit to stand, balance or stair climbing
- be available in full text to the author and published in English between 1990 and January 2010, including electronic publications made ahead of press. Conference proceedings and alike were excluded due to their inability to provide sufficient information to address the second review question.

2.3.2 Information Sources

Electronic databases were searched via Ovid (including Ovid MEDLINE, PsycINFO, Cumulative Index to Nursing and Allied Health Literature, Allied and Complementary Medicine Database, and Evidence Based Medicine Reviews databases), Scopus and EBSCOhost. The search terminology used for the database searches were defined using the PICO framework [78] and are outlined in 2.4.1 and 2.5.1 respectively. To ensure all forms of the searched terminology were included; truncation and wild card characters were used. The reference lists of included studies and recent systematic reviews were also screened and author searches undertaken to identify other relevant studies.

2.3.3 Study Selection

The reviewer (NS) screened the titles of the sourced articles to ascertain their relevance to the review. The abstracts of the selected articles were then read. If it was not clear whether a study should be included the full text was reviewed in depth. If the reviewer could not reach a decision, a second reviewer (DT) was consulted. The full text versions of the articles that met the inclusion criteria were then assessed.

2.3.4 Assessment of Study Quality

The quality of the studies was evaluated by extracting the PEDro scores from the Physiotherapy Evidence Database (www.pedro.org.au). Any studies which did not have a PEDro score were independently rated by two reviewers (NS & DT) with any disagreements being discussed until consensus was reached. The PEDro score considers the studies' characteristics in relation to internal validity including; random allocation, concealment of allocation, comparability of groups at baseline, blinding of patients, therapists and assessors, analysis by intention to treat and adequacy of follow-up and the sufficiency of statistical analysis including; between-group statistical comparisons and reports of both point estimates and measures of variability. Articles were considered high quality if they obtained a score ≥6/10 [79], noting that the maximum a therapy intervention is likely to achieve is 8/10, as it is difficult to blind patients and therapists in most rehabilitation studies.

2.3.5 Synthesis of Findings

A proforma was developed to extract relevant information of interest from each of the studies. Data in relation to the study aims, design and sample were gathered. For the purposes of these reviews the time since stroke was defined as acute (>3 months), sub-acute (3-9 months) and chronic (<9 months). Details of outcome measures related to locomotor ability; whether significant gains in locomotor ability were reported and the magnitude of those gains were also gathered. The details of each of the interventions with particular reference to the parameters of training (type, duration, frequency, dose, intensity, progression and muscle groups/tasks trained) were recorded. A synthesis of findings was undertaken focusing on: the response to the intervention, the training parameters and the extent to which the training parameters met current exercise and rehabilitation recommendations.

2.4 Strength Training

Strength training has been advocated for clinically stable stroke survivors for the past 10 years; most recently in the American Heart and Stroke Association's, "Physical Activity and Exercise Recommendations for Stroke Survivors" [80] and in the NZ "Guidelines for the Management of Stroke" [81]. Strength training is defined as exercise involving repeated muscle contractions against a load with the aim of improving muscle strength, endurance and/or power. The load is usually provided by the individuals' body weight, elastic devices such as Theraband®, free weights, machine weights or isokinetic systems such as the Biodex®. Progressive resistance strength training (PRST) is strength training carried out against an external load (rather than body weight), at a specified intensity, where the resistance is adjusted throughout the training programme [82]. The American Heart and Stroke Association currently recommends that strength training be conducted for 1–3 sets of 10–15 repetitions of 8–10 exercises on 2-3 days per week for people with stroke [80].

This systematic review asked the questions;

> *Is lower limb strength training effective at improving locomotor ability in people with stroke?*

> *What are the training parameters utilised in the research when applying lower limb strength training to improve locomotor ability in people with stroke?*

2.4.1 Search Terms

Figure 2-1 provides the search terms used to search for relevant evidence to address these questions. Details of the search strategy are provided above in Section 2.3.

AND	Search Terms
Population	Stroke
Intervention	exercis* strength* resist* program* NEAR therap* train* OR
Outcome	walk* gait* mobility locomot* ambulat* balance stand* stair climb* OR
Study design	randomised controlled trial randomized controlled trial clinical trial RCT comparison study random* comparative study OR

Where * is the truncation format used in the specific database.

Figure 2-1 Strength Training: Search Terms

2.4.2 Search Results

Electronic database searching yielded 912 articles, of which 279 were duplicates. Title and abstract review reduced the output to 28 articles. Following full text review 11 randomised controlled trials (RCTs) [83-94] were identified which met the inclusion criteria. A summary of study selection is provided in Figure 2-2. Articles excluded on full text were excluded for a lack of randomisation (e.g. [95]), lack of an appropriate control

intervention (e.g. [35, 96]) and a failure to meet the specified definition of strength training (e.g. [95, 97, 98]).
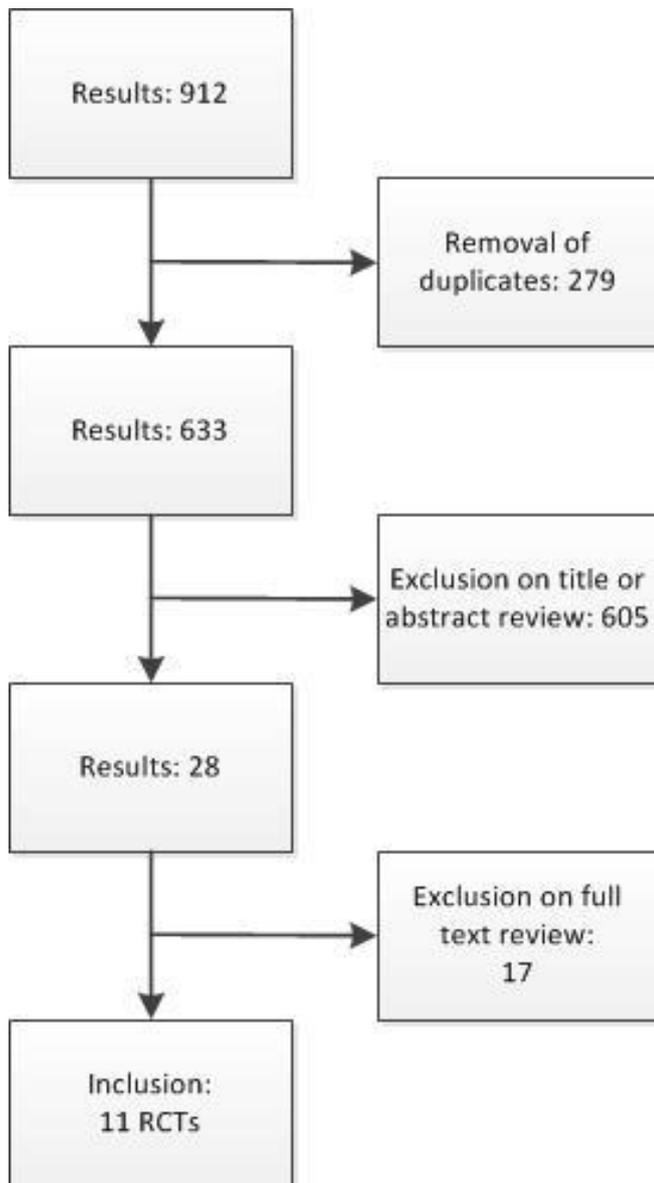
Figure 2-2 Strength Training: Flow Chart of Search Results

This systematic review yielded a total cohort of 507 participants of whom 207 were randomised to a strength training intervention. Sample sizes ranged from 13 [99, 100] to 133 participants [101]. Participants included those still undergoing inpatient rehabilitation [101] through to those living in the community some time since stroke [33, 92, 102]. Table 2-1 provides details of the study, study outcomes and quality.

The quality of the studies was high, with just one study [99, 100] scoring below 6/10 on the PEDro scale. Locomotor abilities assessed included walking speed (n=8) [33, 87, 99,

100, 102-105], walking endurance (n=7) [33, 34, 86, 92, 101-103], balance (n=3) [92, 102, 103], stair climbing (n=4) [33, 34, 87, 99, 100] and sit to stand (n=2) [104, 105]. The comparison intervention was a sham or passive intervention in five studies [33, 34, 101, 104], usual care in five [86, 99, 100, 102, 103, 105] and an upper limb intervention in one study [92].

Studies measured strength in a variety of ways including isometric or isokinetic dynamometry [86, 87, 99, 100, 103], a 1-RM [33], handheld dynamometry [92, 105] and muscle power [104]. Eight of nine studies which measured strength reported gains in strength [33, 34, 86, 87, 92, 99, 100, 103, 105]. Six of the 11 studies reported gains in one or more locomotor ability [34, 92, 99, 100, 102-106]. The most frequently reported gain was in walking speed, with four of eight studies which evaluated walking speed reporting gains in response to the intervention in favour of the strength training group. Gains ranged from 0.18m/s [103]to 0.25m/s [99, 100], with a mean between group difference ranging from 0.08m/s [103] to 0.26m/s [99, 100]. Two of the seven studies which evaluated walking endurance reported gains in favour of the strength training group, reporting mean between group differences of 26.1m and 28.2m respectively on the six minute walk test (6MWT) [92, 103]. Whilst one of four studies which investigated gains in stair climbing [34] and one study which investigated balance, reported small gains in favour of the strength training group [103]. No between group differences in favour of the control intervention were reported.

Table 2-1 Strength Training: Study Details, Quality and Outcomes.

	Sample	PEDro	Intervention (In addition)	Control	Locomotor outcomes	Primary Outcome	Gains in strength	Pre-Post	Between groups	Retention
Duncan 1998 [102]	n=20 Chronic phase	7/10	Mixed (CV endurance)	Usual Care	CWS, 6MWT, BBS	Not specified	Not tested	Yes (CWS=0.25m/s)	Yes (CWS=0.16m/s)	N/A
Teixeira-Salmela 1999 [100, 107]	n=13 Sub-acute to Chronic phase.	3/10	Mixed (CV endurance)	Waitlist control	CWS Stair climbing	CWS	Yes	Yes (CWS=0.24m/s)	Yes (CWS=0.26m/s)	N/A
Kim 2001 [87]	n=20 Sub-acute to Chronic phase	7/10	Isokinetic	Passive movement in Isokinetic dynamometer	CWS, FWS, Stair climbing	CWS Stair climbing	Yes	No	No	N/A
Duncan 2003 [103]	n=92 Sub-acute	8/10	Mixed (Task training, CV endurance)	Usual care	BBS, FR, CWS, 6MWT	Not specified	Yes	Yes (CWS=0.18m/s, BBS=4.36, 6MWT= 61.61m)	Yes (CWS=0.08m/s, BBS=2.72, 6MWT=28.21m)	N/A

Notes: Pre-post= Statistical significant difference post intervention, Between group= Statistical significant difference between the groups, Retention=Gains retained at follow up, UCC= Usual care control, CWS=Comfortable walking speed, FWS=Fast walking speed, 6MWT=Six minute walk test, BBS= Berg balance scale, 2MWT=Two minute walk test, TUAG=Timed up and go, MAS=Motor assessment scale, STS=Sit to Stand, FR=Functional reach. N/A= Not assessed

	Sample	PEDro	Intervention (In addition)	Control	Locomotor outcomes	Primary Outcome	Gains in strength	Pre-Post	Between groups	Retention
Moreland 2003 [101]	n=133 Acute to sub-acute phase	8/10	Functional strength training	Same exercises without resistance	2MWT	2MWT	Not tested	No	No	No
Ouellette 2004 [33]	n=52 Chronic phase	7/10	High resistance	Passive movement and flexibility	6MWT, CWS, FWS, CST, Stair climbing	Not specified	Yes	No	No	N/A
Pang 2005 [92]	n=63 Chronic phase	8/10	Mixed (CV endurance)	Upper limb programme	6MWT, BBS	Not specified	Yes	Yes (6MWT=64.5m)	Yes (6MWT=26.1m)	N/A
Mead 2007 [104]	n=66 Chronic phase	7/10	Mixed (CV endurance)	Relaxation	CWS, Walking Economy, Functional Reach, STS, TUAG	Not Specified	No	Yes (CWS, Walking economy and TUAG- magnitude unclear)	Yes (Walking economy and TUAG- magnitude unclear)	Yes

Notes: Pre-post= Statistical significant difference post intervention, Between group= Statistical significant difference between the groups, Retention=Gains retained at follow up, UCC= Usual care control, CWS=Comfortable walking speed, FWS=Fast walking speed, 6MWT=Six minute walk test, BBS= Berg balance scale, 2MWT=Two minute walk test, TUAG=Timed up and go, MAS=Motor assessment scale, STS=Sit to Stand, FR=Functional reach. N/A= Not assessed

	Sample	PEDro	Intervention (In addition)	Control	Locomotor outcomes	Primary Outcome	Gains in strength	Pre-Post	Between groups	Retention
Bale 2008 [105]	n=18 Sub-acute (Rx=8 UCC=10)	7/10	Functional strength training	Usual care	%WB, CWS, MAS (STS, walk)	N/A	Yes	Yes (CWS=0.23m/s)	Yes (CWS=0.15m/s)	N/A
Flansbjer, 2008 [86]	n=24 (Rx=15 UCC=9)	6/10	Isokinetic	Usual care	FWS, TUAG, 6MWT	Not specified	Yes	Yes (TUAG=5.5s, 6MWT=22m)	No	Yes TUAG
Lee 2008 [34]	n=52	8/10	High resistance	Sham	6MWT, CWS, FWS, Stair climbing	Not specified	Yes	Yes (Stair climbing=14.8W)	Yes (Stair climbing=13.9W)	N/A

Notes: Pre-post= Statistical significant within group difference post intervention, Between group= Statistical significant difference between the groups, Retention=Gains retained at follow up, UCC= Usual care control, CWS=Comfortable walking speed, FWS=Fast walking speed, 6MWT=Six minute walk test, BBS= Berg balance scale, 2MWT=Two minute walk test, TUAG=Timed up and go, MAS=Motor assessment scale, STS=Sit to Stand, FR=Functional reach. N/A= Not assessed

Inspection of the training parameters described in each of the studies indicated that strength training was included as a component of a broader intervention in four studies, encompassing cardiovascular endurance training and/or task-specific training [92, 99, 100, 102-104], while the remaining studies investigated strength training in isolation [33, 34, 86, 87, 101, 105]. No mixed intervention studies were powered to detect the effect of different components of the intervention. The principle method of strength training involved body weight exercises with or without additional weight in six studies [92, 99, 101, 102, 104, 105], machine weights in two studies [33, 34], Proprioceptive Neuromuscular Facilitation patterns resisted by therapist or Theraband® in two studies [102, 103] and isokinetic dynamometers in two studies [86, 87]. The duration of intervention ranged from four weeks [105] to 19 weeks [92], with a total dose of 10 [105] to 57 hours [92]. The total number of exercises completed and the muscle groups targeted was often difficult to interpret as most authors did not give complete descriptions of the intervention. The intensity of the intervention was variable and descriptions frequently lacked detail or quantification of progression parameters [92, 101, 103, 104].

Table 2-2 Strength training: Training Parameters

	Type	Duration (weeks)	Frequency (per week)	Dose (hours)	Intensity	Muscles trained
Duncan 1998 [102]	Mixed Strengthening involved PNF patterns, Theraband and body weight exercises.	12	3	54	When subjects could complete 2 sets of 10 repetitions resistance was increased by progression of Theraband elasticity or by increased manual resistance.	Lower limb exercises in PNF patterns.
Teixeira-Salmela 1999 [99, 100, 107]	Mixed Strengthening involved body weight, sand bags, Theraband	10	3	45	Initiated at 50%1-RM progressed to 80% 1-RM in the 2nd week, continued at this level for the remainder of the intervention.	Hip Flexors and extensors Knee flexors and extensors Ankle plantar and dorsi flexors
Kim 2001 [87]	Isokinetic dynamometer. Concentric	6	3	13.5	Maximal effort	Hip Flexors and extensors Knee flexors and extensors Ankle plantar and dorsi flexors
Duncan 2003 [103]	Mixed Strengthening involved PNF patterns, and Theraband exercises.	12-14	3	54	Once exercise was completed with little difficulty, the resistance of the band used was increased.	Lower limb exercises in PNF patterns

	Type	Duration (weeks)	Frequency (per week)	Dose (hours)	Intensity	Muscles trained
Moreland 2003 [101]	Body weight exercises with added weights	Approx. 8	3	Approx. 12	Moderate exertion Added weights were 0.3-8kg.	Lower limb exercises were designed to be performed in functional patterns of movement.
Ouellette 2004 [33]	Machine pneumatic resistance and pulley exercises	12	3	Not specified. Approx. 27 hours	70% 1-RM. Re-assessed twice weekly	Hip and knee extensors, Ankle plantar and dorsi flexors
Pang 2005 [92]	Mixed Strengthening involved body weight exercises	19	3	57	Increasing biomechanical challenge	Lower limb muscles, mainly hip and knee extensors and ankle plantar flexors
Mead 2007 [104]	Mixed Strengthening was body weight exercises for lower limbs.	12	3	45	Progressing from four to 10 reps by Week 12, changing the biomechanics of the task. As determined by the trainer.	Knee and hip extensors
Bale 2008 [105]	Body weight exercises with added weights	4	3	10	1 set of 10-15 repetitions to moderate fatigue	Lower limb muscles
Flansbjer, 2008 [86]	Isokinetic dynamometer	10	2	30	6-8 repetitions at 80% maximum, two minute rests between sets. As many sets as possible	Knee flexors and extensors

	Type	Duration (weeks)	Frequency (per week)	Dose (hours)	Intensity	Muscles trained
Lee **2008 [34]**	Pneumatic resistance machines, free weights and isometric actions	10-12	3	36	50%1-RM increased to 80%1-RM by week 2. Increased by 3% of 1-RM each session. 1-RM assessed every two weeks.	Lower limb extensors; knee extensors and flexors and plantar flexors

Notes: 1-RM= 1-Repetition maximum

Review of the training parameters against current guidelines indicates that five studies failed to meet the recommendations for strength training in stroke [80] all due to an insufficient number of exercises [86, 92, 104]. Seven studies [86, 92, 101-105] failed to meet the recommendations for strength training in healthy older adults [108]; one due to an insufficient number of exercises [86], two due to insufficient intensity of training [101, 105], and a further four due to both insufficient intensity and number of exercises [92, 102-104].

Table 2-3 Strength Training: Adherence with Guidelines

	PRST	Stroke	Older Adults
Duncan 1998 [102]	No	No Insufficient number of exercises.	No Insufficient intensity and number of exercises.
Teixeira-Salmela 1999 [99, 100, 107]	Yes	Yes	Yes
Kim 2001 [87]	Yes	Yes	Yes
Duncan 2003 [103]	Yes	No Insufficient number of exercises	No Insufficient intensity and number of exercises
Moreland 2003 [101]	Yes	Yes	No Insufficient intensity
Ouellette 2004 [33]	Yes	Yes	Yes
Pang 2005 [92]	No	No Insufficient number of exercises	No Insufficient intensity and number of exercises
Mead 2007 [104]	No	No Insufficient number of exercises.	No Insufficient number of exercises and intensity.
Bale 2008 [105]	Yes	Yes	No Insufficient intensity
Flansbjer 2008 [86]	Yes	No Insufficient number of exercises.	No Insufficient number of exercises.
Lee 2008[34]	Yes	Yes	Yes

Note: PRST=Progressive resisted strength training

2.4.3 Discussion

The purpose of this systematic review was to consider whether lower limb strength training is effective at improving locomotor ability in people with stroke and to describe and evaluate the training parameters utilised in the research when applying lower limb strength training to improve locomotor ability in people with stroke. This systematic review has highlighted that whilst strength training increases strength following stroke its effect on locomotor abilities are equivocal. The review also indicates that past studies of strength training in people with stroke have frequently failed to carry out the intervention in a manner which meets currents recommendations or which are likely to translate into significant gains in locomotor ability in people with stroke.

The evidence base investigating strength training of the lower limbs to improve locomotor ability after stroke includes ten high quality, randomised controlled trials RCTs [83-92] and one study of lesser quality [99, 100]. However, a number of these studies are not powered to detect a difference in the outcomes under investigation [34, 86, 87, 100-102, 105]. There are also two recent systematic reviews [72, 73] and a large body of cohort studies investigating strength training after stroke which provide additional evidence [96, 106, 107, 109-114].

Studies clearly demonstrate marked increases in muscle strength in response to strength training [33, 34, 86, 87, 92, 99, 100, 103, 105], with some studies describing gains from baseline in excess of 65% [34, 86, 87, 105]. A single study which reported no gains in strength in response to strength training conducted strength training at a very low intensity and volume and was likely insufficient to induce adequate overload [104]. Gains in strength also appear to be specific to the muscle and action trained [34, 96]. The maintenance of strength gains has been demonstrated for up to six months post-intervention [86], although most studies fail to follow up participants to assess retention of gains.

The evidence for changes in locomotor ability in response to strength training are less clear, with some studies demonstrating significant gains in locomotor ability [34, 92, 99, 100, 102-106] while others do not [33, 86, 87, 101]. Gains have been reported in walking speed [99, 102, 105], walking endurance [34, 35, 86, 102], stair climbing ability [34, 100, 102, 104] and balance [103]. The most frequently reported gain was in walking speed, with four of eight studies which evaluated walking speed reporting gains in response to strength training. The mean between group differences ranged from 10%(0.08m/s) [103] to 28% (0.26m/s)[99, 100] improvement from baseline. The lower bound of this

magnitude of change does not exceed the reported minimally clinically important difference in CWS of 0.16m/s [115]. Very few of the studies which evaluate walking endurance, stair climbing ability or balance report gains in these abilities in favour of the strength training group. Therefore, the effect of strength training on locomotor ability appears equivocal and when gains in locomotor ability are reported they are modest in size.

A striking finding of this review is the failure of many studies to conduct strength training within the parameters recommended. Five studies [86, 92, 104] failed to meet the current recommendations for strength training in stroke [80], most often in relation to the number of exercises prescribed. The guidelines recommend eight to ten exercises [80], presumably this would equate to a minimum of four exercises for the lower limbs. However, many studies have few strengthening exercises, particularly when part of a mixed intervention, and consequently target a limited number of lower limb muscles. Given the specificity of response to the muscle and action being trained [34, 96]; some of the disparity in the extent of gains seen in locomotor ability may relate to a failure to train relevant lower limb muscles. Review of the muscles trained during strength training suggests that the muscles selected are not always well related to the functional limitations which are being targeted. For example if the intention is to improve walking speed and endurance it seems reasonable to advocate that hip flexors and ankle plantar flexors be targeted in strength training [43, 45, 50], however many studies focus primarily on the hip and knee extensors [33, 34, 86, 92, 101, 104]. There also appears to be limited consideration of the action of the muscle being trained and its specificity to function; with little mention of the range of joint motion and speed of action (muscle power). Closer adherence to the guidelines with regard to the number of exercises and a greater specificity in relation to muscles selected for training and their action, in particular a focus on muscle power, may result in better gains in function.

Whilst current stroke exercise and rehabilitation guidelines make no recommendation in relation to the intensity of strength training [80], the American College of Sports Medicine recommends moderate to high intensity effort to ensure adequate gains in strength in healthy older adults; describing the level of effort as equivalent to 5-6 for moderate intensity and 7-8 for high intensity on a 0-10 point scale. [108],. Strength training in people with stroke is frequently conducted at very low intensities. Six of the eleven studies evaluated [92, 101-105] failed to meet the recommendations for intensity of strength training in healthy older adults [108]. It therefore seems likely that strength gains in people with stroke are limited by an inadequate intensity of training. This may also

explain some of the limited effect of strength training on locomotor ability in people with stroke.

One explanation for the failure to conduct strength training at an intensity sufficient to engender adequate overload may be the types of exercises selected. The strength training intervention or component involved body weight exercises with or without additional weight in five studies [92, 99, 101, 104, 105] and Proprioceptive Neuromuscular Facilitation patterns with applied resistance in another two studies [102, 103]. Body weight and therapist resisted exercises do not lend themselves well to high levels of resistance or progressive overload. Review of the exercises prescribed and training parameters in some studies clearly indicates that loads were insufficient to substantially increase strength in most people with stroke [92, 101, 104, 105].

Five studies included strength training as a component of a broader intervention, encompassing task-specific training and/or cardiovascular endurance training [92, 99, 100, 102-104]. These studies appeared more likely to report positive outcomes in locomotor ability [92, 99, 100, 102-104]. However, it is unclear which component of the treatment causes the treatment effect in these mixed interventions or whether there is in fact an interaction effect between the component parts. Very little is known about the effect of combining locomotor interventions; nor the best way in which to combine them. No studies were identified which compared strength training, task-specific training and cardiovascular training and attention and dose matched combinations of these interventions to definitively determine whether combined interventions are more effective than either single modality intervention. However, one study which did not meet the criteria for inclusion in this review has indicated that there is a risk of over training if sufficient rest days are not provided with combined training [35].

In summary, whilst the evidence base for strength training after stoke indicates that strength training increases strength; the evidence with respect to locomotor abilities is less clear. The findings of this systematic review are supported by a recent meta-analysis investigating physical fitness training after stroke which indicated that there is still insufficient evidence to draw conclusions about the efficacy of strength training on locomotor ability [116]. Therefore, in spite of the relationship between strength and locomotor function, and the capacity of strength training to increase strength after stroke, strength training of lower limb muscles has not yet proved to be an effective intervention to improve locomotor function in people following stroke. In part this failure to induce an improvement in locomotor ability may relate to the intensity and specificity of strength training utilised. However, researchers may also consider whether practice structure and

integration of strength training with other forms of training, such as task-specific training may facilitate the transfer of strength gains to function.

2.5 Task-specific Training

Task-specific training is a commonly used and evidence based rehabilitation approach to improve locomotor ability following stroke. Task-specific training is the repetitive practice of relevant functional motor skills, such as repeated sit-to-stand practice or repeated walking practice [117]. Task-specific training has been advocated in the NZ "Guidelines for the Management of Stroke" [81] and has been the subject of two recently published systematic reviews [74, 75].

For the purposes of this review the definition of task-specific training was restricted to repetitive practice of locomotor skills without the use of therapeutic adjuncts such as body weight supported treadmill training and robotic locomotion devices. This review asks;

Is task-specific training effective at improving locomotor ability in people with stroke?

What are the training parameters utilised in the research when applying task-specific training to improve locomotor ability in people with stroke?

2.5.1 Search Terms

Figure 2-3 provides the search terms used to search for relevant evidence to address these questions. Details of the search strategy are provided above in Section 2.3.

AND	Search Terms
Population	Stroke
Intervention	motor*, task* **Near** relearn*, train*, therap*, specific*, practice*, related **OR**
Outcome	walk*, gait*, mobility, locomot*, ambulat*, stand*, stair climb* **OR**
Study design	randomised controlled trial, randomized controlled trial, clinical trial, RCT, comparison study, random*, comparative study **OR**

Where * is the truncation format used in the specific database.

Figure 2-3 Task-specific Training: Search Terms

2.5.2 Search Results

Electronic data base searching yielded 1734 articles, of which 426 were duplicates. Title and abstract review reduced the output to 77 articles. Following full text review 11 RCTs were identified which met the inclusion criteria. Articles excluded on full text review were excluded for a lack of appropriate control intervention (e.g. [118]), intervention which focused on a single aspect of locomotor ability (e.g [119]), a large portion of the intervention focused on the use of therapeutic adjuncts to apply task-specific training (e.g.

[120]) or a comparison intervention which was considered task-specific training (e.g. [121]). Figure 2-4 outlines the flow of studies through the selection process.
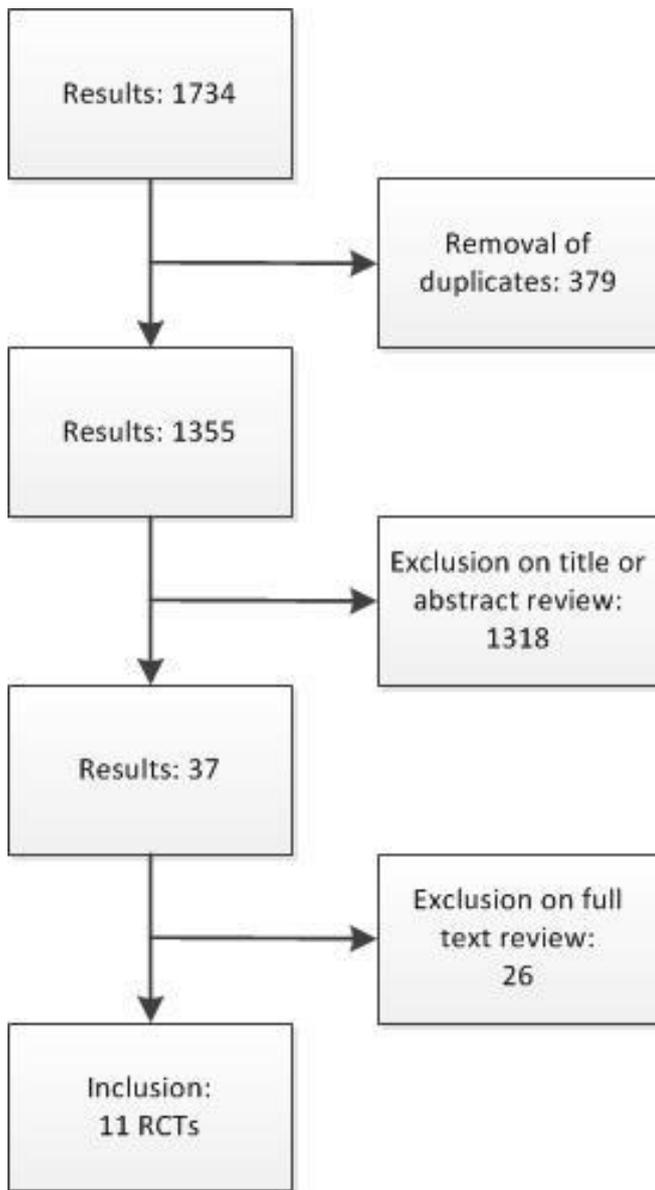
Figure 2-4 Task-specific Training: Flow Chart of Search Results

The eleven studies identified included a total cohort of 697 with 331 randomised to a task-specific-training intervention. The sample sizes ranged from 12 to 120 and included people with stroke throughout the spectrum of time since stroke. The quality of the available evidence was high with ten of the 11 studies rating 6/10 or higher on the PEDro scale. The locomotor abilities measured as outcomes included; walking speed (n=7) [36, 71, 97, 103, 122-124], walking endurance (n=6) [36, 97, 103, 123-125], balance (n=7) [36, 97, 103, 123, 126, 127], walking capacity (n=2) [122, 126] and the timed up and go

(TUAG) which is a composite of sit to stand, walking and turning (n=5) [36, 97, 123, 125, 127].

Ten of the eleven studies were attention and dose matched, with only Yang and colleagues using a no treatment control group as a comparison [97]. Control interventions included; upper limb therapy (n=4) [123, 125, 126, 128], interventions deemed to have low or no relevant motor effects (n=4) [103, 122, 124, 127], and alternative physiotherapy approaches (n=2) [71, 129].

All studies reported gains in locomotor ability in response to the intervention, with nine [36, 97, 103, 122-126, 128, 129] of the eleven studies reporting statistically significant differences in favour of the task-specific training when compared to the control group. The reported gains in walking speed ranged from 0.09m/s [97] to 0.65m/s [122], with the mean between group difference ranging from 0.08m/s [103] to 0.28m/s [122]. Gains in walking endurance were reported by six studies [36, 97, 103, 123-125], with a mean change in response to intervention of between 19m [124]and 221m [125] as measured by the 6MWT. The mean group difference in favour of the task-specific training intervention was between 18m [124] and 116m [125]. Gains in favour of the intervention group were also reported for balance [97, 103, 123, 125], walking capacity [122] and the TUAG [97, 125].No between group differences in favour of the control intervention were reported.

Table 2-4 Task-specific Training: Study Details, Quality and Outcomes

	Sample	PEDro	Intervention (In addition)	Control	Locomotor outcome	Primary Outcome	Pre-Post	Between groups	Retention
Kwakkel 1999 [122]	n=101 Acute	7/10	Individualized (+/- Treadmill training, +/- strengthening)	Airsplint	FAC, CWS	FAC	Yes (FAC=4, CWS=0.65m/s)	Yes (FAC=1, CWS=0.28m/s)	Yes
Dean 2000 [123]	n=12 Chronic	5/10	Group circuit training (Strengthening, Treadmill)	Upper limb circuit training	CWS, 6MWT, Step test, TUAG	Not specified	Yes (6MWT=42.1m, CWS=0.12m/s, Step test=3.6 reps)	Yes (6MWT=37.4m, Step test=3.3 reps)	Yes
Langhammer 2000 [129]	n=60 Acute to Sub-acute	6/10	Individualized motor relearning programme (Not specified)	Individualized Bobath approach	MAS	MAS	Yes, although MAS also includes upper limb function (MAS=13 pts)	Yes, although MAS also includes upper limb function (MAS=4 pts)	UTA
Duncan 2003[103]	n=92 Sub-acute	8/10	Group circuit training (Strengthening,, CV endurance)	Relaxation	BBS, FR, CWS, 6MWD	Not specified	Yes (CWS=0.18m/s, BBS=4.36, 6MWT= 61.61m)	Yes (CWS=0.08m/s, BBS=2.72, 6MWT=28.21m)	N/A
Blennerhassett 2004 [125]	n=30 Acute to sub-acute	8/10	Group circuit training (CV endurance)	Group upper limb circuit class	6MWT, Step te st, TUAG	Not specified	Yes (6MWT=221m, TUAG=12.8s, Step test=6 reps)	Yes (6MWT=116m, TUAG=7.6ss, Step test=2.6 reps)	Yes

Notes: Pre-post=Statistically significant difference post intervention, Between group= Statistically significant difference between the groups, Retention=Gains retained at follow up, CWS=Comfortable walking speed, FWS=Fast walking speed, 6MWT=Six minute walk test, BBS= Berg balance scale, TUAG=Timed up and go, MAS=Motor assessment scale, FR=Functional reach, N/A= Not assessed, UTA=Unable to assess.

	Sample	PEDro	Intervention (In addition)	Control	Locomotor outcome	Primary Outcome	Pre-Post	Between groups	Retention
McClellan, 2004 [126]	n=26 Subacute to chronic	7/10	Prescribed home programme with tele support	Upper limb prescribed home programme	FR, MAS-Walk	Not specified	Yes (FR=4.5cm)	Yes (FR=7.7cm)	Yes
Salbach, 2004 [36, 128]	n=91 Sub-acute to Chronic	8/10	Circuit training (Treadmill)	Upper limb circuit class	6MWT, CWS, FWS, BBS, TUAG	6MWT	Yes (6MWT=40m, CWS=0.14m/s, FWS=0.20m/s)	Yes (6MWT=35m, CWS=0.11m/s, FWS=0.21m/s)	N/A
Marigold 2005 [127]	n=61 Chronic	6/10	Agility group	Stretching and weight shifting (TaiChi)	BBS, TUAG	Not specified	Yes (BBS=4.4pts, TUAG=3.5s)	No	Yes
vanVliet, 2005 [71]	n=120 Acute to sub-acute	7/10	Movement science based physiotherapy	Bobath	RMA, MAS, CWS	RMA	Yes (UTA)	No	Yes (UTA)
Yang 2006 [97]	n=48 Chronic	7/10	Individualized circuit training. (Emphasis on increasing strength)	No treatment	CWS, 6MWT, Step test, TUAG	Not specified	Yes (CWS=0.09m/s, 6MWT=40.6m, TUAG=1.7s)	Yes (CWS=0.09m/s, 6MWT=34.3m, Step test = 2.6reps, TUAG=1.8s)	N/A
Mudge, 2009 [124]	n=58 Chronic	7/10	Group circuit training	Social and educational classes.	Step watch monitor, CWS, 6MWT, RMI	Step watch monitor	Yes (6MWT=19m)	Yes (6MWT=18m)	Yes CWS

Notes: Pre-post=Statistically significant difference post intervention, Between group= Statistically significant difference between the groups, Retention=Gains retained at follow up, CWS=Comfortable walking speed, FWS=Fast walking speed, 6MWT=Six minute walk test, BBS= Berg balance scale, TUAG=Timed up and go, MAS=Motor assessment scale, FR=Functional reach, N/A= Not assessed, UTA=Unable to assess.

The training parameters outlined in each of the studies is described in Table 2-5. Task-specific training was provided in a one on one approach in six studies [36, 71, 97, 122, 126, 129] and in a group setting in five studies [103, 123-125, 127]. A circuit training approach, applied either in a group or one on one, was used in six studies [36, 97, 103, 123-125], whilst three studies reported the development of an evidence based practice guideline or intervention protocol to guide intervention implementation [71, 122, 129]. The duration of training ranged from three [129] to 20 weeks [122], with a total dose ranging from three [126] to 54 hours [103]. The intensity of training was not specified in five studies [71, 122, 126, 127, 129], four studies described the intensity as being customised to the individual by the therapist [97, 123-125], whilst one study reported having structured criteria for progression although the details were not reported [103]. No studies specifically quantified the intensity of training. The tasks trained were reported in eight studies; most studies included a breadth of tasks including sitting, sit to stand, standing balance, stepping and walking tasks [103, 122-125, 127, 128], whilst three studies appeared to focus primarily on standing balance and stepping tasks [97, 126, 127]. Two studies did not provide details of the intervention [71, 129].

Table 2-5 Task-specific Training: Training Parameters

	Type	Duration (weeks)	Frequency (per week)	Dose (hours)	Intensity	Tasks trained
Kwakkel 1999 [122]	Individualized Based on evidence based practice guideline	20	5	50	Not specified	Sitting, Standing, weight-bearing in standing and walking, emphasizing stability and speed.
Dean, 2000 [123]	Circuit class	4	3	12	Graded by physiotherapist. Participants encouraged to work as hard as possible.	Sit and reach, sit to stand, stepping, heel lifts, standing with narrow base of support, stand-walk-return, walking negotiating surfaces, obstacles, slopes and stairs
Langhammer, 2000 [129]	Motor relearning programme	3 (Duration of inpatient stay; shorter for the intervention group)	5	Minimum approx. 10	Not specified	Not specified
Duncan 2003 [103]	Circuit class	12-14	3	54	Structured protocols for the exercise tasks, criteria for progression (not detailed)	Step-ups, sit to stand, balance tasks, marching, toe rises, kicking a ball, simulated sports and walking tasks.
Blennerhassett, 2004 [125]	Circuit class	4	5	20	Not specified. Customized and progressed to suit the individual	Sit to stand, stepping, obstacle course, walking, standing balance tasks.
McClellan, 2004 [126]	Home programme with video instructions and telephone support	6	N/A	3	Not specified	Not detailed. Aimed to improve mobility in balance and walking. Twenty three hierarchical exercises, final exercises stepping backward and off a step.

	Type	Duration (weeks)	Frequency (per week)	Dose (hours)	Intensity	Tasks trained
Salbach, 2004 [36, 128]	Circuit training	6	3	18	Challenged to maximize performance.	Ten tasks aimed at increasing strength and speed, balance and distance of walking. Task included; Step ups, walking, walking backwards, walking with narrow base, kicking ball, Figure 8 walking, obstacle course, walking and carrying, speed walking and stairs.
Marigold 2005 [127]	Agility class	10	2	20	Not specified	Dynamic balance tasks; standing balance, tandem walking, Figure 8 walking, stepping, obstacles, sit to stand with sensory manipulation.
vanVliet 2005 [71]	Movement science based physiotherapy. Individual with therapist and/or assistant	Not specified; as per usual inpatient rehabilitation practice.		Variable, Median=6	Not specified	Not specified
Yang 2006 [97]	Circuit training	4	3	6	As hard as possible. Graded by therapist to participants functional level.	Stand and reach, sit to stand, stepping, heel rise.
Mudge 2009 [124]	Group circuit training	4	3	12	Graded to participants ability and progressed as tolerated.	Task orientated gait or standing balance tasks or strengthening of lower limbs in task-specific way.

2.5.3 Discussion

The evidence base for task-specific training to improve locomotor ability after stroke includes ten high quality studies and one study of lesser quality [123]. A number of these studies are well powered to detect differences in locomotor outcomes [36, 103, 122]. The evidence base is further supported by two recent systematic reviews with meta-analyses [74, 75] and a large body of research which investigates task-specific training using therapeutic adjuncts such as treadmill training [35]. In most studies selected for this review the comparison intervention was attention and dose matched with either; interventions expected to have no impact on locomotor ability [36, 103, 122-128] or other physiotherapy treatment approaches [71, 129].

When compared to attention and dose matched interventions expected to have no impact on locomotor ability, task-specific training results in greater gains in locomotor ability; as seen in measures of walking speed, endurance and functional capacity. However, reported gains in walking speed following task-specific training are modest in sub-acute and chronic stroke participants (0.0m/s to 0.21m/s) [36, 103, 123, 124]. When compared to control interventions, gains in favour of the task-specific training intervention are just zero to 0.11m/s in the sub-acute to chronic stroke population [36, 71, 103, 123, 124]. This finding suggests that gains in walking speed in response to task-specific training are limited; this assertion is supported by a recent meta-analysis which estimated the effect size as small [130, 131]. However, gains in walking speed in favour of the task-specific training group may be greater when the intervention is initiated early after stroke [122]. Reported improvements in walking endurance following task-specific training vary between 19m and 116m in the 6-MWT [36, 97, 103, 123-125], with much greater gains reported in two studies where people were treated earlier after stroke and at higher doses [36, 125]. In studies that measured balance gains in favour of the intervention group were reported for all [97, 103, 123, 125, 126] but one study [36]. However, it is not clear whether the magnitude of the gains reported represent clinically significant improvements [132]. The modest gain in walking speed, endurance and balance reported in most studies following task-specific training may not reflect a gain which exceed the level of error and variability in the measures [132-134] or represent a meaningful difference in terms of locomotor ability for people with stroke [135].

When compared to alternative physiotherapy approaches such as the Bobath approach, evidence in support of task-specific training is less clear cut. One study reports marked differences between the task-specific training intervention and the control intervention in favour of task-specific training [129], while another shows no difference between the

interventions [71]. However these studies are challenged by a failure to clearly describe and delineate between the interventions. For example; in vanVliet's study no description of the intervention content was provided and the task-specific training intervention was carried out by physiotherapists who required training in the intervention by the first author because they had insufficient experience of task-specific training [71]. Therefore, there appears to be insufficient evidence to recommend task-specific training over other physiotherapy approaches; however more robust investigation of comparative interventions is required.

The research evidence provides little guidance in relation to the optimal training parameters for implementation of task-specific training. Training programmes tend to be of short duration, with most being six weeks or less [36, 71, 97, 118, 123-126, 129]. The total dose of training ranges from three hours contact with a physiotherapist [126] to more than 50 hours [122]. It is unclear what the appropriate dose of task-specific training is required to ensure permanent changes in locomotor ability, although there are some indications of greater benefits with larger doses of task-specific training [130, 131]. Gains in locomotor ability may be more modest the greater the time since stroke [97, 123, 124, 126], although this assertion has not been supported on meta-analysis [130, 131]. An important limitation of these studies is that they generally fail to quantify the intensity of training or parameters for progression of exercises. The intensity of training is an important consideration as evidence in healthy populations indicates that motor learning is promoted by task complexity [136], suggesting that ensuring that training is sufficiently challenging maybe a key training parameter in task-specific training.

Most studies included a breadth of locomotor tasks from sit to stand through to complex walking tasks. However those studies which focused primarily on balance tasks reported no or modest gains in other locomotor abilities such as walking [97, 126, 127], indicating limited transfer of training beyond the specific tasks trained. This notion is further supported by Salbach and colleagues' work [36, 128]. They showed no gains in balance ability as measured by the Berg balance scale in response to task-specific training but significant gains in balance self-efficacy, which were correlated with improvements in walking endurance [128]. The authors noted the task-specific nature of gains in both locomotor ability and self-efficacy; where participants reported increased self-efficacy and demonstrated increases in locomotor ability in those tasks which were trained, but not those which were not [128]. Mudge and colleagues add a further dimension to this concept; they demonstrated that whilst gains in walking endurance were found in response to their intervention, no gains in usual walking activity ensued. This indicates

that not only the actual task but also the context in which practice is undertaken maybe important in driving locomotor changes following task-specific training [124].

In summary, based on the current research evidence task-specific training is more effective than attention controlled interventions which are not aimed at improving locomotor ability. However, there is insufficient evidence to assert that task-specific training is more effective than other forms of physiotherapy which are aimed at improving locomotor ability. Task-specific training results in only modest gains in locomotor ability in people after stroke, particularly those in the sub-acute to chronic phase and gains appear to relate to the actual tasks trained.

2.6 Summary

The main findings of these systematic reviews are that:

- Strength training results in considerable increases in muscle strength.
- Strength gains appear to translate poorly into the recovery of locomotor ability.
- In part, this may be explained by a failure to strength train people with stroke at sufficient intensity and with specificity to their locomotor disability.
- Task-specific training improves locomotor ability; however gains are modest at best.
- Gains in locomotor ability following task-specific training appear to relate to the actual tasks trained.
- Little is known about the most effective training parameters for task-specific training.

Chapter 3   Scientific Underpinnings

3.1 Prologue

Recent literature has criticised rehabilitation research in general [137], and locomotor rehabilitation research ability specifically [16, 138], for being insufficiently grounded in scientific evidence. Therefore, this chapter focuses on recent advances in the understanding of neural control of walking and neural plasticity in response to rehabilitation.

3.2 Introduction

As outlined in Chapter 2 the most effective method of rehabilitation to enhance locomotor ability has yet to be determined [14]. However, both strength training and task-specific training have potential as effective rehabilitation strategies. This chapter focuses on recent advances in our understanding of neural control of locomotion and neural plasticity in response to strength training and task-specific training interventions, which may further inform the development of rehabilitation strategies to improve locomotor ability after stroke [139, 140].

3.3 Neural Control of Walking

As a complex locomotor skill walking requires control of multiple muscles and the capacity to modify movement in response to the changing demands of the task and the environment. Early research into walking using spinalised and decerebrate animals emphasised the role of spinal central pattern generators in the control of walking [141, 142]. Central pattern generators are spinal networks capable of generating basic locomotor rhythmic motion without afferent or cortical input [143]. However, evidence from people with spinal cord injury has highlighted that whilst central pattern generators likely exist in humans, they are too weak to induce walking without some form of stimulation (i.e. sensory input or electrical stimulation of the spinal cord)[143]. Therefore, the notion that walking in humans is an automatic movement which is largely under spinal control has been challenged. In humans it seems that subcortical and cortical structures play an important role in the control of walking.

Recent imaging and TMS studies in humans have investigated supraspinal contributions to the control of walking. Spectroscopy imaging studies highlight the diffuse activation of the higher centres during walking, including the frontal cortex, premotor and supplementary motor areas, sensory and primary motor cortices, basal ganglia and cerebellum [144, 145]. TMS studies have specifically demonstrated the role of the primary motor cortex and its influence on muscle activity during walking [141, 146, 147]. An elegant study by Petersen and colleagues demonstrated that alteration of cortical excitability of lower leg muscles in healthy humans using subthreshold TMS results in reduced muscle activity in the targeted muscle during walking [148]. This finding clearly indicates the contribution of descending input from the motor cortex to the leg muscles. The importance of cortical input to walking is further emphasised by the considerable limitations which are seen in walking in humans in response to cortical damage, such as stroke.

Imaging studies suggest that when walking at a comfortable speed, cortical inputs are less pronounced in the control of walking. However, when increases or decreases in speed are imposed on a person, there is greater activation of cortical structures, particularly the sensorimotor cortex [149]. At this point in time, research investigating the neural control of walking provides limited information about the modulation of walking in more complex situations such as obstacle negotiation and with secondary tasks. In all likelihood locomotion in the complex community environment requires even greater cortical input than laboratory walking over smooth ground or treadmill walking studies elucidate [149].

Afferent input is also important for control of walking, it provides feed forward information to enable modulation of movement for upcoming environmental and task challenges [150]. Afferent information also enables the modulation of motor output and correction of errors in response to changes in limb load and position [151]. Studies in humans indicate that this afferent information is used to correct errors in walking at both spinal and supraspinal levels [143, 152].

Alterations to the neural control of walking after stroke have been investigated using imaging techniques [149, 153]. These studies emphasise asymmetric activation of the sensorimotor cortex, with reduced output from the lesioned cortex, and recruitment of other cortical areas including the premotor cortex and prefrontal areas during walking in people with stroke. The changes in activation and the relative recruitment of diffuse and ipsilateral networks appears dependent on the severity of the stroke; with greater recruitment of the internal capsule, basal ganglia and premotor cortex seen in people with more severe strokes [149].

In summary, investigations into walking emphasise the distributed neural control of walking; which requires afferent, spinal, subcortical and cortical inputs. Walking in more challenging situations requires greater cortical input. Recent research investigating the neural control of walking in people with stroke emphasises the asymmetric nature of sensorimotor cortices activation and the recruitment of diffuse and ipsilateral networks to achieve walking following stroke.

3.4 Neural Plasticity

Neural plasticity is thought to be the biological basis for many of the improvements in motor impairment and locomotor ability seen in response to rehabilitation after stroke [138, 154-156]. Neural plasticity describes the capacity of the nervous system to adapt in response to changes in demand, and includes changes at the genetic, biochemical, intracellular, intercellular and structural levels of the nervous system [157, 158]. Animal studies, and imaging and TMS studies in humans suggest that neural plasticity following stroke may include; re-mapping of areas adjacent to the lesion, harnessing previously redundant networks, recruitment of diffuse and ipsilateral networks to re-route past the lesion, and changes in the excitability of inter and intra-hemispheric, sub-cortical and spinal networks [1, 158, 159].

For improvements in neural plasticity to be meaningful for an individual they need to be positive and long term in nature [159]. The spectrum of changes seen in neural plasticity extends from short term changes in synaptic potentiation which alter neural excitation through to, long term potentiation which is associated with motor learning [16, 160]. Evidence from the neuroscience literature provides considerable information in relation to neural plasticity in response to strength training and task-specific training in healthy people and people with stroke.

There is evidence to demonstrate that task-specific training promotes neural plasticity in both healthy and stroke populations [161-164]. A large body of evidence in healthy people describes short and long term neural plasticity in response to different forms of task-specific training in various populations using EEG, imaging and TMS [136]. These studies highlight that greater neural plasticity is promoted by greater task complexity and more repetitious practice [136, 156, 165-167]. Studies investigating neural plasticity in response to lower limb tasks have demonstrated adaptations at both cortical and spinal levels in healthy people, although most studies point to greater changes at the cortical level in response to complex task-specific training [165, 168-171]. Cortical adaptations as a result of practice of a complex skill rather than a simple skill include increased cortical

excitability, reduced activation thresholds, and an enhanced shift from cortical control to subcortical control as the task becomes highly learnt [136]. A recent study highlights that increases in corticomotor excitability in response to task-specific training are task dependent and may not be seen in similar but untrained tasks [169].

In people with stroke, neural plasticity in response to task-specific training has been demonstrated following treadmill walking [172-175]. Immediate increases in corticomotor excitability in response to treadmill walking have been demonstrated, with greater increases seen in those who had previously completed a body weight supported treadmill training (BWSTT) rehabilitation programme [176]. Yen and colleagues demonstrated increased cortical representation of lower limb muscles in response to additional BWSTT during rehabilitation in people with chronic stroke [173]. Improvements in walking in response to BWSTT have been associated with improved symmetry in the activation of the sensorimotor cortices, increased activation in the ipsilesional premotor cortex during walking [177] and increased activity in both sensorimotor cortices and in midline cortical regions such as the supplementary motor area [178].

Evidence of neural adaptations to strength training in healthy people is provided by research which demonstrates that; a) strength increases early in a strength training programme prior to muscle hypertrophy, b) that there are gains in strength on the contralateral side during unilateral strength training and c) that gains in strength are seen in response to motor imagery of strength training tasks [171, 179, 180]. Strength training in healthy people has been shown to alter corticomotor excitability, reduce motor unit recruitment threshold and change motor unit firing patterns [179-182]. No studies were identified which categorised long term changes in neural plasticity in response to strength training in people with stroke. However, in healthy people [183-190] and people with stroke [191-193] during submaximal and maximal unilateral muscle contractions, such as those utilised in strength training, there are transient increases in cortical and spinal level excitation. Increases in corticomotor excitability may be specific to the trained action and not seen at rest [169, 171], emphasising the specificity of neuroplastic responses to strength training. There are also indications that whilst strength training leads to increased corticomotor excitability, excitation does not necessarily extend to all the cortical areas that are important for more complex task performance [166]; this may explain why strength training alone is insufficient to drive large gains in locomotor ability. This transient increase in corticomotor excitability in response to strength training may be sustained after the termination of exercise for up to ten minutes, although most of the effect is lost quickly after the cessation of exercise [183-187].

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The transient increase in corticomotor excitability seen in response to strength training suggests a potential role for unilateral strength training of the affected side to act as a priming intervention prior to task-specific training. Priming interventions are interventions which aim to alter the excitability of the nervous system to enhance neural plasticity during subsequent training. Priming interventions in people with stroke which are currently being investigated include repetitive TMS, Transcranial Direct Current Stimulation, somatosensory stimulation, motor imagery and various movement paradigms in the upper limb [194, 195]. In stroke it has been shown that performing a movement priming task in the upper limb prior to a task-specific training leads to improved outcome compared to a control group who received only task-specific training [194]. No similar works in the lower limb relating to the priming effects of movement were identified. However, the applicability of this concept is supported by sports science literature which indicates that performing a movement at a maximal or near maximal effort produces a priming stimulus resulting in improved task performance [196-198]. Further support from the athletic training literature demonstrates that combining strength training with sports specific training can enhance performance outcomes in elite athletes [199-202].

3.5 Summary

In summary, research into neural control of walking indicates that both spinal and cortical centres are considered important [142, 203, 204]. There is evidence that task-specific training modifies cortical activation, resulting in long-lasting neuroplastic changes [205, 206]. There is further evidence that strength training modifies spinal [180, 190] and cortical activation [190]. By using unilateral strength training on the affected side to prime the nervous system prior to task-specific training in a structured and systematic way, we may see the benefits of facilitating excitation in both spinal and cortical networks prior to inducing use-dependent neural plasticity specific to locomotor abilities.

Therefore, the premise of Strength for Task Training (STT) is that combining; unilateral progressive resisted strength training to improve strength and prime the CNS, with task-specific training (TST) to induce permanent neuroplastic changes, will promote greater gains in locomotor function than either PRST or TST on their own.

Chapter 4   Defining the Intervention

4.1 Prologue

Chapter 2 described the evidence base for both strength training and task-specific training to improve locomotor ability after stroke, highlighting some of the limitations in the application of both strength training and task-specific training to date. Chapter 3 described the evidence from the neuroscience literature in relation to the neural control of walking and neural plasticity which informed the conceptualisation of the STT intervention. This chapter defines the intervention and describes the modelling process and consultation undertaken to develop the Strength for Task Training (STT) intervention prior to pilot testing.

4.2 Introduction

Following original conception of the intervention in response to the evidence base and neuroscientific literature a structured approach to intervention development was undertaken. This process was in keeping with the Medical Research Councils (MRC) recommendations for the development and evaluation of complex interventions including modelling of process [22]. Initial modelling involved defining the key features of the intervention; then a period of consultation with key stakeholders was undertaken. Consultation extends the MRC recommendations further by ensuring early identification of issues which might influence the efficacy, acceptability and translatability to clinical practice. Following consultation a final version of the intervention was prepared for piloting, along with relevant intervention resources.

4.3 Defining Features of the Intervention

The STT intervention was designed to harness the priming effects of strength training and maximise the effects of strength and task-specific training for improving locomotor abilities. The defining features of this intervention were:

1. Strength training is utilised to systematically prime the central nervous system prior to task-specific training.
2. Strength training and task-specific training are conducted in an evidence based manner to maximise gains in locomotor ability.

The defining features of the intervention are discussed in more depth below.

4.3.1 Priming

As discussed in Chapter 3 priming interventions are interventions which aim to alter the excitability of the nervous system to enhance neural plasticity during subsequent training. The STT intervention utilises the fact that unilateral sub-maximal and maximal muscle contractions cause an increase in corticomotor excitability which is specific to the muscle activated and the manner in which it was trained. To be effective as a priming intervention for task-specific training, the unilateral strength training intervention needed to be conducted in a muscle and during an action which was directly relevant to the task being trained. Further, the task-specific training needed to be undertaken in a timeframe which would maximally utilise the priming effect. As much of the increase in corticomotor excitability is lost within the first few minutes following strength training, the transition between strength and the relevant task training needed to be prompt.

4.3.2 Training Parameters

Given that review of the literature indicated that both strength training and task-specific training are frequently undertaken using training parameters which may fail to generate the maximum gains in locomotor ability, particular attention was given to the training parameters for each intervention. It was intended that;

PRST be applied in an evidence based manner including;

- In a muscle(s) relevant to the specific locomotor skill of interest
- With specificity of type of action and speed of movement to the trained locomotor skill
- In a progressive manner
- At a dose and intensity sufficient to induce significant increases in strength

TST be applied in an evidence based manner including;

- Utilising locomotor skills which are relevant to community locomotion
- With specificity to the contexts and environments fundamental to community locomotion
- In a progressive manner
- At a dose and intensity sufficient to induce significant and long term increases in locomotor ability

Relevance

To ensure that the intervention was relevant to locomotion the tasks identified as important for task-specific training were selected with reference to those skills needed to achieve community locomotion [27-29, 207-209]. The muscles selected for strength training were then chosen by identifying the prime movers for each locomotor task. Reference was made to studies investigating the kinematics of locomotor skills in stroke and healthy populations [210-214] and the primary impairments which affect locomotor ability in people with stroke [53, 215-218].

Specificity

As discussed in the literature review, specificity of training is a key parameter in both strength and task-specific training. Specificity was applied to the task-specific training by considering the types of contexts and environments in which locomotor skills are utilised, particularly in relation to the environment and types of secondary tasks undertaken [27-29, 207-209, 219]. The specificity of strength training was considered by referencing the type and speed of action undertaken by the muscle(s) in the given task; kinematic studies in healthy and stroke populations were used to guide this [210-214, 220] and, where possible, the strength training exercise was designed to match the in-task muscle action as closely as possible [53, 215-218].

Intensity

Review of the literature indicated that both strength training and task-specific training are frequently undertaken at low intensities. Therefore an important training parameter for the intervention was to set the intensity of training such that people were working at moderate to high intensities. Whilst considerable guidance in relation to intensity of training was available for strength training from recommendations in healthy populations [108, 221] and some previous work in people with stroke there was far less guidance for task-specific training. No assessment tools or outcome measures of task intensity or difficulty were identified in the review of the literature, nor were any recommendations for how intensity of training should be prescribed during task-specific training. Therefore, we developed a method for establishing and progressing training intensity. Participants were presented with a colour coded visual analogue scale which rated task difficulty from 'Very, very easy' through to 'Very, very difficult'.

Progression

To guide progression in strength training, recommendations in healthy older adults and healthy adults were used [108, 221]. Strength training was progressed from moderate intensity to high intensity and then an element of power training was introduced.

For task-specific training reference was made to the reviewed literature as described above along with literature related to motor learning [219, 222-225]. Particular consideration was given to sensory manipulation and secondary tasks [226-228], the provision of feedback [223, 229] and practice structure [219]. Nine parameters were identified for the progression of task-specific training; two which related to practice structure (part vs. whole task and blocked vs. random practice), three which related to the motor difficulty of the task (speed, accuracy, biomechanical challenge), one which related to the availability of sensory information, two which related to the imposition of secondary tasks (cognitive tasks and physical tasks) and one which related to changing the environment that practice was carried out in.

Dose

Frequency, duration of training and rest periods were considered to ensure that the total dose of intervention was likely to be sufficient to maximise over load without inducing over training and negative symptoms [35, 221]. The total dose of intervention was determined based findings in both task-specific training literature [36, 125] and strength training in healthy populations [221].

4.3.3 Draft Intervention for Consultation

Based on the defining features of the intervention the following draft intervention parameters were recommended for consultation.

High intensity strength and task-specific training; where progressive resisted strength training is undertaken immediately prior to task-specific training of locomotor skill (as outlined in Table 4-1 below) and the muscle which is strength trained is a prime mover in the skill which is being trained. The recommended intervention period was 12 weeks, with three 1-hour sessions per week in a group of eight people with stroke (n=8) supervised by a NZ registered physiotherapist and therapy assistant.

Table 4-1 Draft STT Intervention

Station	PRST Component	TST Component
1	Quadriceps	Sit-to-stand-to-sit
2	Hamstrings	Walk backwards
3	Hip Extensors	Stairs
4	Hip Abductors	Walk sideways
5	Hip Flexors	Walk (comfortable speed)
6	Plantarflexors	Walk (fast speed)
7	Dorsiflexors/Evertors	Obstacles

4.4 Consultation

The consultation process involved presenting the draft intervention parameters described above to the following groups for feedback.

4.4.1 Rehabilitation Experts

The intervention and design for the method of the larger RCT study was initially developed in consultation with motor control, exercise science and rehabilitation experts. Refer to the Acknowledgements for a list of these people. These experts met to review the intervention concept and offer advice in relation to the process required for development and staged evaluation of the intervention.

4.4.2 People with Stroke

A group of six people with stroke were invited to participate in a Stroke Advisory Group. These people represented a diverse group with stroke, and included those who lived independently in their own homes to those in private hospital care, younger adults to those aged over 85 years and people from various cultural backgrounds including Maori, people who were employed, retired, managing families and beneficiaries. One group meeting and a number of one-on-one meetings with the Stroke Advisory Group were undertaken. In the group meeting the background to the intervention and the draft intervention were presented to the group and they were asked to provide feedback about the concept and specifics of the intervention.

The Stroke Advisory Group were strongly supportive of the intervention and the planned research, particularly; the value of focusing on interventions to improve locomotor ability following stroke, the benefits of group based interventions for enhancing motivation and the importance of identifying effective interventions in the period following discharge from in-patient rehabilitation. The groups input can also be seen through the explicit inclusion of a two week familiarisation period at the outset of the intervention, and the inclusion of 'getting up from the floor' and 'ramps' in the task-specific training which were identified as key locomotor skills often over looked in rehabilitation.

The NZ Stroke Foundation was also consulted through the Chief Executive and the Field Officers of the Northern Region. Consultation with the Stroke Foundation highlighted the importance of disseminating the results to ensure uptake of the intervention, if successful, by physiotherapists and the need to develop resources for people with stroke who are unable to access rehabilitation services. In addition, the demands placed on people with stroke through financial challenges (particularly relevant to intervention and transport costs) was highlighted, along with the timeframe in which many people realise they need more help following their stroke (approximately three months) and the effects of lassitude and fatigue on motivation. The Stroke Foundation was supportive of the development of an intervention that could help to improve the locomotor ability, quality of life and participation of its members.

4.4.3 Neurological Physiotherapists

As the intervention was designed for implementation by neurological physiotherapists, a group of five experienced clinicians working in this field were consulted on three occasions. Refer to the Acknowledgements for a list of these people. This group provided feedback in relation to the timing of intervention with respect to discharge from hospital services, the details of the strength training component and the need to be able to modify and support exercise to ensure good movement patterns, issues of safety around supervising a group of eight people with stroke who are exercising at high intensity/with high levels of difficulty, the level of expertise required to implement the intervention, the suitability of hospital outpatient and community environments to support rehabilitation programmes involving strength and task-specific training in a real world context.

4.5 Resource Implications

The final phase of the intervention development gave consideration to the available resources at AUT University and the requirements for space and equipment to implement

the intervention. This included developing a list of potential exercises, progressions and required equipment, along with testing of each of the exercises and modelling of transitions of participants through the intervention programme. This process aided in the development of the intervention recording form and the physiotherapists training manual which are described below. Following the consultation process and consideration of resource implications the final version of the STT intervention was prepared for pilot testing.

4.6 Intervention for Piloting

4.6.1 Basic Framework

The STT intervention involved unilateral progressive resistive strength training of a relevant muscle group on the affected side immediately followed by locomotor task-specific training. STT is a group based exercise programme carried out on three alternate days per week for one hour. The intervention period lasts for twelve weeks, with a total planned dose of rehabilitation of 36 hours. Each group of five participants was supervised by one NZ registered physiotherapist with clinical experience in stroke rehabilitation and one Therapy Assistant.

The programme included a two week familiarisation period followed by ten weeks of moderate to high intensity physical rehabilitation, where intensity of training was increased in a stepwise manner over the course of the intervention. The basic programme content is described in Table 4-2 below. Participants complete up to three circuits of seven exercise stations during the hour, with each station comprising one set of the PRST exercise, a maximum transition time of 30 seconds followed by two minutes of TST of a related locomotor ability.

Table 4-2 STT Programme Content

Station	PRST Component	TST Component
1	Quadriceps (Seated leg press)	Sit-to-stand-to-sit
2	Hamstrings (Westminster Pulley)	Walking backwards
3	Hip Extensors (Westminster Pulley)	Stairs / Getting off Floor
4	Hip Abductors (Theraband)	Walking sideways
5	Hip Flexors (Rotary Hip)	Walking (comfortable speed)
6	Plantarflexors (Supine Leg Press)	Walking (fast speed) / Ramps
7	Dorsiflexors/Evertors (Theraband)	Obstacles

The PRST component enabled two familiarisation weeks for participants to achieve a 14RM (approximately 60%1-RM). The RM is set by having participants rate their perceived exertion (RPE) for the final repetition on the Borg scale of perceived exertion [230]. If their RPE fell below 18 the load was increased to maintain the desired RM. From weeks three to eight the target RM reduced every two weeks such that by week eight participants are working at an 8RM (approximately 80% of 1-RM). In week nine the load was reduced by 20% to approximately 60% of 1-RM and the participant were asked to push as hard and as fast as possible to introduce a power element.

Task-specific training was progressed across nine parameters which reflect alterations to motor task difficulty (speed, accuracy and biomechanical challenge), sensory availability, practice structure (part versus whole task practice, blocked versus random practice), the imposition of secondary tasks (cognitive and physical) and changes to the environment. Each parameter had up to eight possible progressions or modifications to enable the physiotherapist to tailor the task difficulty to the individual. Task-specific training will be progressed based on the participants' perception of task difficulty and was undertaken at a 'Somewhat Difficult' intensity initially and progressed to 'Very Difficult' intensity by week nine. Task difficulty was determined by having the participants rate the difficulty of the task on a scale from 'Very, very Easy' to 'Very, very Difficult'. In addition a number of progression requirements were imposed; by week five some tasks needed to be conducted with reduced sensory availability and some with a secondary task, by week nine some tasks needed to be practiced in a random practice structure and some in alternative

environments such as outside or in the corridor. An example of all the available progressions or modifications for the tasks stair climbing and sit to stand are provided below. The progressions were not intended to be strictly hierarchical but reflect all the parameters of training that the physiotherapist could potentially modify and offer scope for considerable variability in practice.

Table 4-3 Stair Climbing Task Progressions

Task	Speed	Accuracy	Sensory	Biomechanical	Cognitive	Physical	Environment	Practice
Single Step	Self-selected	No change	No sensory manipulation	Step 15cm	Talking	Cup	Inside gym	Blocked
Stairs	Increased	Step end on	Thin Foam	Step 30cm	Count up in 3's, 7's	Full cup	Stairwell	Random
Step Ladder	Maximum	Narrow path	Vaseline smeared glasses	Step 45cm	Get xxx$ from wallet	Tray of glasses	Outside	
		Line	Slow head turns	With rail/hand support	Answer telephone	Full washing Basket		
			Combined any two	Two stairs at time with rail	Words beginning with…	Packed suitcase		
				No rail		Shopping bags		

Table 4-4 Sit to Stand Task Progressions

Task	Speed	Accuracy	Sensory	Biomechanical	Cognitive	Physical	Environment	Practice
Standard Seat	Self-selected	N/A	No sensory manipulation	Standard BoS	No cognitive task	No physical task	Inside gym	Blocked
Low Seat	Increased		Thin foam	Narrow BoS	Talking	Cup	Outside	Random
Office Chair	Maximum		Thick foam	Step stance	Counting up in 3's, 7's	Full cup	Maximum distractions	
Lounge Chair	Slow		Vaseline smeared glasses	Tandem stance	Words beginning with…	Plate and cutlery		
Bar Stool			Blindfold		Operate Radio Controlled car	Shopping bags		
All chairs			Slow head turns			Full washing basket		
			Fast head turns					
			Combined any two					

Note: N/A= Not applicable, BoS= Base of support

4.6.2 Resources

To facilitate implementation of the STT intervention and to ensure intervention fidelity a number of resources were developed.

Training Manual

A training manual and resource was developed for the physiotherapists and therapy assistants. Refer to Appendix A for a copy of the training manual. This manual was intended to support the physiotherapists one-on-one training and included;

- The theoretical basis of the intervention
- The programme content and structure
- The specifics of each exercise and the relevant progressions
- Details of the kinematic emphasis for individual strengthening exercises along with the key compensations to be avoided
- Logistics of a single training session including the timing and transitions between exercises
- Orientation to the gym environment and equipment
- Methods for monitoring participants and documenting individual and group responses
- Strategies for managing risks including emergency protocols and adverse events reporting

Treatment Planning and Documentation

In addition to the training manual the intervention implementation was supported by a detailed electronic intervention planning and documentation form. This Excel® spreadsheet enabled the treating physiotherapist to plan the ensuing intervention and print a paper copy to hand to the participant at the beginning of each training session. For the PRST component the documentation included the weight/resistance used, the number of repetitions undertaken per set and the RPE on the final repetition. For the TST component the documentation included the training undertaken across the nine parameters of the task with each available progression or modification selected via a drop down menu, and the participants rating of perceived difficulty for each task and any comments from both the participant and the physiotherapist. Participants and physiotherapists recorded the number of sets completed and any comments. See below for an example of a completed form.

	Participant Name:													
	Date:	Fri 26.08.11												
			Select a level for each parameter of the task by clicking on the cell and selecting from the drop down box.											
			Once complete; click "Save As" and Save the file using the Participant Initials and date eg. NS_23_7_2011											

EXERCISE GROUP	TASK	RPE	Part vrs. Whole	Speed	Accuracy	Sensory Availability	Biomechanical Challenge	Attention-Cognitive	Attention- Physical	Environment	Blocked vrs Random	Task Sets	Comments
1	Leg Press- Quadriceps	19	150kg	Set_1_Reps=8	Set_2_Reps=7								
	Sit_Stand_Sit	18	Low_Seat	Slow	N/A	Combined_Any_Tw	Tandem Stance	Cognitive -up 3's, 7	No physical task	Inside Gym	Blocked	2	Thin foam + blindfold
2	Hamstrings	19	Weight=10 kg	Set_1_Reps=8	Set_2_Reps=8								
	Backwards_Walking_Tu	16	Backwards_Wa	Max_Speed	Line	Combined_Any_Tw	Large_Step_Length	Cognitive -up 3's, 7	No physical task	Inside Gym	Blocked	2	Thick foam + glasses
3	Hip_Extensors	19	11kg	Set_1_Reps=8	Set_2_Reps=8								
	Stairs_Up_from_floor	17	Stairs	Max_Speed	No change	Slow_Head_Turns		Cognitive -up 3's, 7	Shopping Bags	Corridor	Blocked	2	Corridor stairs
4	Hip_Flexiors	19	10kg + BP	Set_1_Reps=8	Set_2_Reps=8								Using baseplate on machine
	Comfortable Walking	16	Walking	Increased	Line	Thick_Foam	Large_Step Length	Cognitive -up 3's, 7	Suitcase	Outside	Blocked	2	
5	DorsinFlexors/Evertors	12	Weight=No Ther	Set_1_Reps=8	Set_2_Reps=8								Gold Theraband
	Obstacles	17	Step Over	Increased	Follow designa	Slow_Head_Turns	Combo Stationary	Cognitive -up 3's, 7	No physical task	Inside Gym	Blocked	2	
6	PlantarFlexors	19	96kg	Set_1_Reps=8	Set_1_Reps=8								
	Fast Paced Walking/Slo	17	Fast Walking	Fast_Speed		Fast_Head_Turns	Self_Selected_Step Len	Cognitive -up 3's, 7	Backpack	Outside	Blocked	2	Wearing Backpack
7	Hip Abductors	19	Weight=No Ther	Set_1_Reps=8	Set_2_Reps=0								Gold Theraband
	Sideways Walking	17	Lateral Step Up	Increased	Line	Combined_Any_Tw	Large_Step Length	Cognitive -up 3's, 7	No physical task	Inside Gym	Blocked	2	Thin foam + glasses

Self_Selected_Step_Length
Small_Step_Length
Large_Step_Length

Comments:	
Working really well.	

Figure 4-1 An Example of the Intervention Recording Form

Gym Posters

Basic posters to cue the participants at each station, along with posters to aid in the evaluation of exercise intensity and to promote high intensity exercise were also developed.
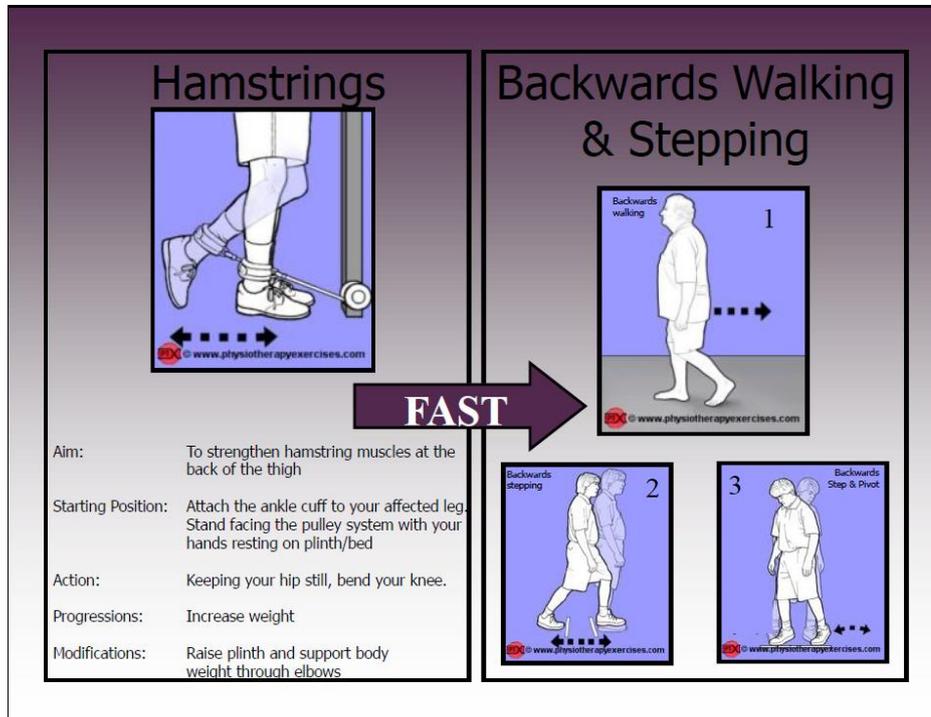
Figure 4-2 Station 2 Poster: Hamstrings and Backwards Walking

Figure 4-3 Gym Poster

4.7 Summary

The development of this novel intervention has been leveraged from the evidence base for strength training and task-specific training following stroke, and grounded in the neuroscience literature to inform its theoretical development and conceptualisation. The defining features of the STT intervention are that it utilises unilateral strength training to systematically prime the central nervous system prior to task-specific training and conducts both strength training and task-specific training in an evidence based manner to maximise gains in locomotor ability. Modelling of process and consultation with key stakeholders resulted in a number of important refinements to the intervention prior to piloting; whilst planned implementation is supported by the development of key resources to ensure intervention fidelity.

SECTION TWO

MEASUREMENT OF NEURAL PLASTICITY IN RESPONSE TO LOCOMOTOR REHABILITATION

Chapter 5   Measurement Selection

5.1 Prologue

In the process of preparing the STT intervention for piloting and planning the research method for a future RCT, it became apparent that identifying suitable measures of neural plasticity in response to locomotor rehabilitation in people with stroke was problematic. This section outlines the process of selecting an appropriate outcome measure of neural plasticity for the clinical trial. 0 describes the feasibility assessment undertaken to identify appropriate outcome measures, whilst Chapter 6 and Chapter 7 describe two repeated-measures studies investigating the test-retest reliability of two potential measures of neural plasticity; BDNF and TMS.

5.2 Introduction

A key consideration in planning a clinical trial is the selection of outcome measures; this is particularly true in a pilot trial where the purpose of the research includes identifying the breadth of possible intervention effects and relationships between intervention effects [15, 23]. It was considered important to select outcome measures across the spectrum of the ICF model to provide a broad view of the intervention effect. While measures of impairment, locomotor ability and participation in stroke were identified which had robust reliability, validity and limited administrative burden [24, 25] (refer to Section 8.3), the identification of suitable measures of the biological processes underlying recovery proved more challenging.

As described in Chapter 3, neural plasticity is thought to be the biological basis for many of the improvements in motor impairment (body structure and function) and functional movement skill seen in response to rehabilitation after stroke [157, 158]. Measurement of aspects of neural plasticity after stroke provides scope to enhance our understanding of the mechanisms of recovery and motor learning after stroke and may aid the refinement of interventions aimed at reducing motor impairment and improving locomotor skills [231, 232].

5.3 Measurement Selection Process

The choice of neural plasticity measure for this research programme was made initially based on an analysis of feasibility; and then consideration was given to the likely participant acceptability and the psychometric properties of the measurement tool. Table 5-1 provides a basic description of each potential measurement tool and the feasibility assessment which considered; the availability of the necessary equipment, the level of local expertise, whether the measurement tool had been previously used in studies investigating neuroplastic changes in response to locomotor rehabilitation following stroke and the likely cost per participant.

Table 5-1 Measures of Neural Plasticity: Analysis of Feasibility.

Measurement Tool	Description	Availability	Expertise	Researched	Cost
Transcranial magnetic stimulation (TMS)	Uses a magnetic field to induce activation of the motor cortex and induce a Motor Evoked Potential (MEP) to reflect corticomotor excitability at rest or during tasks.	✓	✓	✓ [173, 176]	Approximately NZD$50.00
Functional magnetic resonance imaging (fMRI)	Uses MRI to assess deoxyhaemoglobin concentration changes to reflect brain activation during tasks.	✓	✓	✓ [178, 204, 233-235]	Approximately NZD$1,100.00+
Diffusion tensor imaging (DTI)	Uses MRI to assess water diffusion changes to reflect neural pathways at rest.	✓	✓	✓ [236]	Approximately NZD$1,100.00+
Functional near-infrared spectroscopy (fNIRS)	Uses near infrared spectrography to assess changes in cerebral oxygenation and blood flow to reflect brain activation during tasks.	✗	✗	✓ [153]	Not applicable
(Magnetoencephalography) MEG	Uses magnetometers to assess changes in electromagnetic fields to reflect neuronal activation during tasks.	✗	✗	✗	Not applicable
Positron emission tomography (PET)	Uses emission tomography to assess the uptake of various radioactive isotopes to reflect brain activation during tasks.	✗	✗	✗	Not applicable
Brain derived neurotrophic factor (BDNF)	Uses a sandwich enzyme immunoassay (ELISA) to assess the level of BDNF in blood serum or plasma which may reflect neural plasticity.	✓	✓	✗	Approximately NZD$100.00

[231, 237-239]

Based on the feasibility assessment above; fNIRS, MEG and PET were considered unsuitable measurement tools, as the equipment and expertise were not available locally at the time of research planning. fMRI and DTI had previously been used to assess neural plasticity in response to locomotor rehabilitation [178, 204, 233, 234], however these techniques were rejected due to the associated costs. Therefore, TMS and measurement of serum BDNF levels were both considered as potential measures of neural plasticity, because the equipment and expertise was available locally and there was low, cost associated with their use.

The next phase in measurement selection examined the psychometric properties of the measures and their acceptability to potential participants. The psychometric properties considered included validity and reliability. Validity refers to the extent to which a measure measures what it intended to measure. Whereas reliability refers to the reproducibility and internal consistency of a measure [25].

5.4 TMS

5.4.1 Validity

TMS is a non-invasive method of measuring the excitability of the intra-cortical and corticomotor pathways. TMS measurements are routinely used in neuroscience and rehabilitation research to investigate neurological pathology and as a biomarker of neural plasticity following exercise and rehabilitation interventions in healthy and neurological populations [174, 238, 240-242].

While more commonly used in investigations of upper limb [238, 243], TMS has also been used to measure the corticomotor excitability of lower limb muscles after stroke [173, 176, 244-246]. In two small studies, TMS measures of lower limb muscles taken early after stroke were correlated with recovery from motor impairment, but not with recovery of locomotor skills [244, 246]. This finding questions the predictive validity of TMS in relation to regaining locomotor skill. However, investigations of neural plasticity in response to locomotor rehabilitation using TMS have demonstrated improvements in corticomotor excitability of lower limb muscles following rehabilitation when measurements were taken during an isometric contraction [176] and at rest [173]. In one study a correlation between the changes in corticomotor excitability and the degree of functional improvement was demonstrated [173]; suggesting concurrent validity between neural plasticity and improvements in locomotor skill.

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Nevertheless, neural plasticity is very task-specific and measurement at rest or in isometric contractions may not reflect the full extent of neural plasticity associated with rehabilitation of complex motor tasks [232]. Experimental methods applying TMS during different complex motor tasks, such as walking, jumping, standing balance and cycling have recently been developed [146, 169, 247, 248]; whilst logical and ecologically sound, the psychometric properties of these techniques have not yet been evaluated. It is also worth noting that TMS is a specific measure of the corticomotor and intra cortical pathways; measurement parameters may not reflect the full breadth of neuroplastic changes in response to rehabilitation; such as changes in the secondary motor areas, non-motor cortical areas, subcortical structures and the cerebellum. Refer to Table 5-2 for an outline of TMS parameters of corticomotor and intra-cortical excitability.

Table 5-2 TMS Parameters

TMS Parameter	Description
Threshold	The level of stimulation required to produce a MEP in the target muscle in a given number of stimulations, usually five out of ten. Threshold can either be quantified at rest (Resting motor threshold (RMT)) or at a percentage of MVC (Active motor threshold (AMT)).
MEP Amplitude	The amplitude of the evoked EMG activity which results from TMS stimulation, considered a measure of corticomotor excitability. The size of the MEP can be quantified for a given level of stimulation.
MEP Area	The area under the MEP, considered a measure of corticomotor excitability.
MEP Latency	The length of time between stimulation and the onset of a MEP.
Intra-cortical Inhibition (ICI)	Using paired pulse stimulation a suprathreshold stimulus is preceded (1.5-3 ms) by a conditioning stimulus. An indication of the relative contribution local inhibitory of inputs to motor cortex output.
Intra-cortical Facilitation (ICF)	Using paired pulse stimulation a suprathreshold stimulus is preceded (6-10 ms) by a conditioning stimulus. An indication of the relative contribution of local facilitatory inputs to motor cortex output.

[241]

TMS is contraindicated in people who have; a pacemaker, epilepsy, metal implants, skull anomalies, and those who take medications such as tricyclic anti-depressants, neuroleptics and medications which lower seizure threshold [249]. This potentially excludes many people with stroke, particularly those with concomitant medical problems. In addition, TMS has limited usefulness when a MEP in the target muscle cannot be elicited. This frequently occurs in people with moderate to severe stroke due to the effect of the stroke on corticomotor excitability. These factors may limit the external validity of studies using TMS as a measure of neural plasticity due to the inherent selection bias associated with the measurement tool.

5.4.2 Acceptability to People with Stroke

The acceptability of TMS as a measurement tool has not been formally explored in people with stroke. TMS can be uncomfortable, particularly at high stimulator intensities which are often required to elicit a MEP in people with stroke. The literature reports the induction of headaches, facial twitches and discomfort associated with the noise emitted by the stimulator and keeping the head still during testing [249]. Another factor which may influence the acceptability of TMS is the length of time required to gather data, which is often long (1 ½-2 ½ hours). This may be a particular issue for people with stroke who often experience fatigue [250]. TMS requires touching of the head which may not be appropriate in some cultural groups.

5.4.3 Reliability

Studies investigating the reliability of TMS show high test-retest reliability of the upper and lower limb muscles in healthy people [250-252]. However, despite its widespread use in people with stroke, there has been limited consideration of the reliability of TMS measures in this population. Two studies of the reliability of TMS in upper limb muscles in people with stroke demonstrate similar test-retest reliability to healthy participants, but with significantly higher levels of intra- and inter-session variability than seen in healthy participants [250, 253].

One study has investigated the reliability of TMS parameters of the more affected and less affected quadriceps muscle in people with stroke. The researchers investigated motor threshold, MEP amplitude and latency; demonstrating excellent reliability for motor threshold (ICC=0.98), modest reliability for latency (Vastus Medialis ICC=0.69, Vastus Lateralis ICC= 0.79), but poor to modest reliability for MEP amplitude (Vastus Medialis ICC=0.54, Vastus Lateralis ICC= 0.21) on the more affected side [245]. The authors suggest that the poor reliability observed in MEP amplitude may be related to the variability seen in brain activation patterns after stroke. Greater exploration of the variance of the measurement parameters during test-retest may have illuminated this issue further. The poor reliability observed in MEP amplitude may also have related to a failure to adequately standardise the level of muscle activation during testing.

While MEP's obtained during low level voluntary contractions are less variable than those at rest in healthy participants [251, 252], people with stroke have difficulty sustaining a consistent level of force, particularly at low levels of MVC [254, 255]. This may have contributed to the increased variability in TMS seen in people with stroke in this study and

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may account for the poor test-retest reliability of MEP amplitude. The variance may be less during a functional muscle contraction, such as that seen during a locomotor task like walking [252]. Therefore, the reliability of TMS measurement parameters taken during functional motor tasks may have better test-retest reliability than those taken during isometric muscle contractions, particularly in people with stroke. This concept has not been investigated in either healthy people or people with stroke.

5.4.4 Responsiveness

A meta-analysis by Richards and colleagues demonstrated negligible to large effect sizes (range 0.034-1.950) on TMS measures in response to high intensity upper limb rehabilitation interventions in people with stroke [243]. It was possible to calculate effect size in one of the two studies which used TMS to investigate neural plasticity in response to locomotor rehabilitation [173, 176]. In this study, a large effect size in resting motor threshold (ES=1.32) and map size (ES=0.72) in Tibialis Anterior was found when 12 additional BWSTT sessions were added to usual care physiotherapy over a four week period [173]. It is worth noting that the authors did not report results for MEP amplitude or latency.

5.4.5 Interpretability

The interpretability of raw TMS measures are hampered by the fact that measurement methods differ between studies and laboratories. Differences include, but are not limited to: whether the MEP is measured at rest, at a specified level of muscle contraction or during a functional task; the parameters of the stimulation; methods of averaging the data; methods of MEP normalisation and the muscle being investigated.

In cross-sectional studies a comparative group of healthy people is usually included which aids the interpretation of the TMS measurements. However, this is not the case in longitudinal studies investigating treatment effect and generally readers of rehabilitation intervention studies are not familiar with TMS measurement values in normal or pathological populations; making interpretation of TMS measures of neural plasticity challenging. To date no large scale validation studies have been conducted which look at magnitude of change in TMS measures and commensurate changes in locomotor skill; meaning that no assertion regarding minimally clinically important difference can be made.

5.5 BDNF

5.5.1 Validity

BDNF is a protein which has been observed to promote neurogenesis, neuroprotection, neuroregeneration and increase synaptic efficacy and plasticity, particularly in response to exercise and physical activity [256]. However, research investigating changes in BDNF levels in response to physical activity, exercise and rehabilitation in humans and its relationship to other measures of neural plasticity is a relatively new area of scientific exploration [257].

In humans BDNF levels can be measured in both blood plasma and blood serum using a sandwich enzyme immunoassay (ELISA) to indicate circulating levels of BDNF. In healthy adults, more than 70% of BDNF circulating in the blood originates from the CNS [258] and serum concentrations of BDNF are thought to reflect brain tissue BDNF levels [259] .In healthy adults serum and plasma levels of circulating BDNF have been shown to elevate in response to acute exercise and decrease with subsequent rest [256]. Some studies also suggest that basal BDNF levels change in response to ongoing exercise programmes in healthy adults. [258, 260-266]. Similar findings have been reported in people with multiple sclerosis [267, 268]. These findings support the assertion that serum BDNF levels may represent a valid biomarker of neural plasticity. However, BDNF levels have not been previously investigated in people with stroke.

Studies investigating motor learning and neural plasticity in healthy individuals with val66met polymorphism in the BDNF gene provide further evidence of the role of BDNF in the neural plasticity which underpins motor learning. Val66met polymorphism reduces the expression of BDNF in response to physical activity, and individuals with val66met polymorphism have reduced neuroplastic responses to task-specific training and repetitive TMS of the corticospinal circuits[257, 269, 270].. These findings support the construct validity of BDNF as a biomarker of the neural plasticity in response to rehabilitation in humans. However, it should be noted that whilst BDNF levels may act as a biomarker of neural plasticity, the measurement would give no indication of whether plasticity was adaptive (positive) or maladaptive (negative)[157]. For example, following stroke an individual may undertake task specific training of locomotion, if that practice involved motor learning of a compensatory movement pattern such as excessive hip abduction and flexion to achieve foot clearance, measurement of BDNF levels may

demonstrate that the person with stroke experienced a neural plastic adaptation to training but not that the adaption was maladaptive.

In animal stroke models BDNF levels have been shown to change in response to environmental enrichment, exercise and rehabilitation interventions [271-278]. Where exposure to exercise and rehabilitation interventions increases BDNF levels in the hippocampus and other areas of the brain, with associated improvements in motor skill [271-278]. Importantly, when the expression of BDNF is blocked in animal stroke models, the positive effect of rehabilitation on neural plasticity and motor recovery following stroke are negated [275]. These findings illustrate that BDNF has an important role in the neural plasticity underpinning motor learning in response to rehabilitation in animal stroke models; supporting the face validity of BDNF levels as a measure of neural plasticity in response to locomotor rehabilitation in humans.

Participants who are on medications or have medical conditions which adversely affect coagulation may need to be excluded from BDNF testing for safety reasons. This may create a selection bias by excluding people with ischaemic stroke who take Warfarin.

5.5.2 Acceptability to People with Stroke

BDNF testing in humans involves the collection of venous blood via cannulation (needle insertion); people who are averse to needles may not want to engage in this process.

5.5.3 Reliability

The test-retest reliability of BDNF measurement has not been formally explored in healthy people or people with stroke. Reliability testing to date has focused on the laboratory processes associated with quantifying BDNF levels in a given sample. A study by Trajkovska and colleagues [279] reported an inter-assay variability of less than 10%, which is in keeping with the manufacturer's assertion of an inter-assay variability of 8.5%. In the same study the intra-sample variability was reported as 12%; in contrast to the manufacturer's assertion of 3.7% [279]. Nevertheless, these values are considered low for an assay [279].

Focus on the reliability of laboratory processing rather than test-retest reliability of the *entire* testing process negates the influence of biological and technical variability and error on the reliability of the measure. Factors such as diet, stress and activity levels of the individual being tested are all likely to introduce biological variation to the measurement

of BDNF [280]. The repeatability of the collection and preparation method and transportation and storage of samples [279], are also likely to introduce variability and error. Therefore, it is essential to establish the test-retest reliability of the entire BDNF testing process in healthy participants and people with stroke.

5.5.4 Responsiveness

BDNF levels have been shown to elevate in response to acute exercise in healthy adults [258, 260, 261, 263, 264, 266, 268], the magnitude of the response appears to be dependent on the intensity of the exercise intervention [260]. More interestingly, basal and post-acute exercise BDNF levels have been shown to alter in some studies in response to an exercise training programme [265, 267].

5.5.5 Interpretability

The raw values for serum BDNF vary widely in the research literature, with group averages for basal levels ranging from 0.6 ng/mL [261, 266] to 30.9 ng/mL [263]. These differences have in part been ascribed to variations in the way samples are collected, prepared and analysed [279] making interpretation of raw BDNF values challenging.

There are currently no studies which compare BDNF levels in people with stroke to healthy people, nor studies which use BDNF as a marker of neural plasticity when investigating treatment effect in response to rehabilitation intervention. Considerable research work is required to elucidate the interpretation of serum BDNF measures as a biomarker of neural plasticity.

5.6 Summary

A key consideration in planning a clinical trial is the selection of outcome measures. Measurement of aspects of neural plasticity after stroke may provide scope to enhance our understanding of rehabilitation interventions. Two potentially feasible methods of measuring neural plasticity in response to locomotor rehabilitation were identified; TMS-derived measures of corticomotor excitability and blood serum levels of BDNF. The psychometric properties of both techniques have to date been described in a very limited way, therefore attention was given to exploring the test-retest reliability of both TMS and BDNF. The establishment of measurement reliability is the first stage in describing a tools psychometric properties and this information is essential when determining sample and effect sizes in research trials.

Chapter 6   Test-retest Reliability of BDNF Measures

6.1 Prologue

0 described the face validity of BDNF as a biomarker of neural plasticity in response to locomotor rehabilitation and noted that no previous descriptions of the psychometric properties of serum BDNF as a measure of neural plasticity in humans were found in the literature. This chapter addresses the test-retest reliability of BDNF.

6.2 Introduction

The aim of this study was to evaluate the test-retest reliability of blood serum derived measures of BDNF before, during and after a bout of sub-maximal exercise in people with stroke and healthy participants. A secondary aim of the study was to identify any differences in the release of BDNF in response to sub-maximal exercise and the uptake during subsequent rest in people with stroke and healthy participants.

6.3 Method

6.3.1 Study Setting and Design

This study was undertaken at the Health & Rehabilitation Research Institute (HRRI) of AUT University, Auckland, NZ. The study used a repeated measures experimental design where two testing sessions were separated by 7 to 14 days.

6.3.2 Sample

A target sample size of 20 participants per group was selected based on recommendations in the research literature [281] and following consultation with a biostatistician.

Recruitment

Participants were recruited to the study through advertisement in local newspapers, at local Stroke Foundation meetings, via AUT Akoranga campus community and AUT University Physiotherapy Clinics notice boards. In addition a letter of invitation was sent

to those people who had already consented to be contacted in relation to studies being conducted at the HRRI. Those potential participants who expressed an interest in the study were sent an information sheet. Face to face provision of the study information was also offered.

Inclusion Criteria

All participants with stroke who satisfied the following inclusion criteria were considered;

- Over the age of 20 years
- A single stroke with a self-reported hemiparesis affecting the ability to walk
- 6 months or more since the stroke
- Willing to have blood taken before, during and after exercise

Potential healthy participants who meet the following inclusion criteria were considered for the study;

- Over the age of 20 years
- Age range similar to that of the stroke group
- Willing to have blood taken before, during and after exercise

Exclusion Criteria

Potential participants who had any of the following were excluded from the study;

- Unstable heart condition
- Brainstem or cerebellar stroke (non-hemi paretic presentation)
- Unable to walk 10m with or without a walking device
- Co-morbidities that would detrimentally affect the person's ability to participate in a cycle exercise task
- In the stroke group, if the GP has not given medical clearance to participate in exercise.
- Fear of needles.
- Reception of a blood product or blood transfusion within the 4 weeks prior to the study commencing
- Taking medications which adversely affect blood coagulation, such as Warfarin.

6.3.3 Ethical Considerations

Ethical approval was obtained from the Auckland University of Technology Ethics Committee (see Appendix B to Appendix D).

6.3.4 Measures

Brain Derived Neurotrophic Factor

BDNF is a neurotrophin produced in the CNS and peripheral tissues and stored in blood platelets. As it is released in response to exercise and found in blood serum it is possible to measure BDNF in a blood sample before, during and after exercise. Serum derived measures of BDNF were analysed using ChemiKine™ BDNF assay which is a sandwich enzyme immunoassay (ELISA) kit (Millipore Australia Pty Ltd, Sydney). The ChemiKine™ BDNF assay uses rabbit polyclonal antibodies generated against human BDNF and coated onto a microplate which are used to capture BDNF from a sample. BDNF specific, biotin conjugated, mouse monoclonal antibodies detect the captured BDNF. The manufacturers report that the assay has a minimum sensitivity of 7.8pg/mL with an intra-assay variation of ±3.7% (125pg/mL), inter-assay variation ±8.5% (125pg/mL).

Blood Lactate

Blood lactate provides an indication of the physiological response to exercise. Measurement of lactate in plasma was assessed by lactate enzymatic oxidation using a Roche Cobas® Modular P Analyser and the Roche Lactate kit (Cat. No. 11822837). The lower detection limits of the method were 0.22mmol/L with a measuring range of 0.22 to 15.5mmol/L.

Heart Rate

Heart rate was monitored either using pulse oximetry via finger or ear probe, or with Polar heart monitor (Brittain Wynard & Colter Ltd, Auckland, NZ) dependent on participant preference.

6.3.5 Testing Procedure

Two identical testing sessions were held 7-14 days apart. On arrival to the exercise laboratory participants were asked to rest in a seated position for 30 minutes. The purpose of the rest period was to ensure that a resting heart rate was attained and that any exertion from walking to the laboratory did not affect the measures. In the first testing

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session demographic information was gathered during the rest period; including ethnicity, age, sex, time since stroke, type of stroke, and current prescribed medications. Heart rate was recorded at the end of the rest period.

Prior to starting exercise a 20g IV cannula was inserted into either the hand or cubital fossa of the participant; depending on the suitability of venous access. The site of insertion was determined by the phlebotomist in consultation with the participant.

Blood Sampling Procedure

Following cannula insertion a baseline blood sample was taken (10ml), and then transferred to a 5ml SST Vacutainer (BD367954) and a 4ml Fluoride Oxide Vacutainer (BD367935) using a blood transfer device. Each tube was inverted 5-8 times and then labelled with the participants' code and sample number. The labelling was cross checked between the phlebotomist and research assistant and then the tubes were stored on ice. The phlebotomist secured the cannula using Tegaderm® and flushed the cannula with 2ml of heparinised saline.

Subsequent samples were taken just prior to exercise termination (30 minutes) and at the end of the post-exercise rest period. For each sample collection the phlebotomist flushed 2ml of normal saline into the cannula with a new syringe, withdrew 5ml of frank blood into the same syringe, and then discarded the syringe. The Phlebotomist then attached a new syringe and collected 10mL of frank blood, transferring it to a 5ml SST Vacutainer and a 4ml Fluoride Oxide Vacutainer using a blood transfer device. Each tube was then inverted, labelled and stored as described above. After each sample was collected the phlebotomist flushed the cannula with 2mL of heparinised saline and cleaned the luer with an alcohol swab.

Following the final blood sample the phlebotomist removed the cannula, applied pressure to the site and then applied a small dressing as appropriate. Participants were advised not to lift anything heavy with their tested arm for the rest of the day.

Exercise Procedure

The exercise task consisted of a maximum of 30 minutes of exercise on a stationary exercycle, semi-recumbent exercycle, seated pedal or arm crank; dependent on the participants ability and preference. Participants began exercise with a 3 minute warm up and then exercised at a specified intensity for a further 27 minutes. Participants were encouraged to exercise at a perceived rate of exertion (RPE) of 12-14 on the Borg RPE

Scale [282, 283]. This exercise level is equivalent to 55-69% of heart rate maximum [284, 285] and is described as 'somewhat hard'. The American Heart and Stroke Association currently recommend this level of exercise intensity for people with stroke [80].The participants RPE was evaluated every 10 minutes during exercise testing. After 30 minutes of exercise the participant sat and rested for a further 30 minutes. Heart rate was recorded at baseline, at ten minute intervals during the exercise period and at the end of the rest period. Figure 6-1 outlines the timing of the exercise and blood sampling procedures.
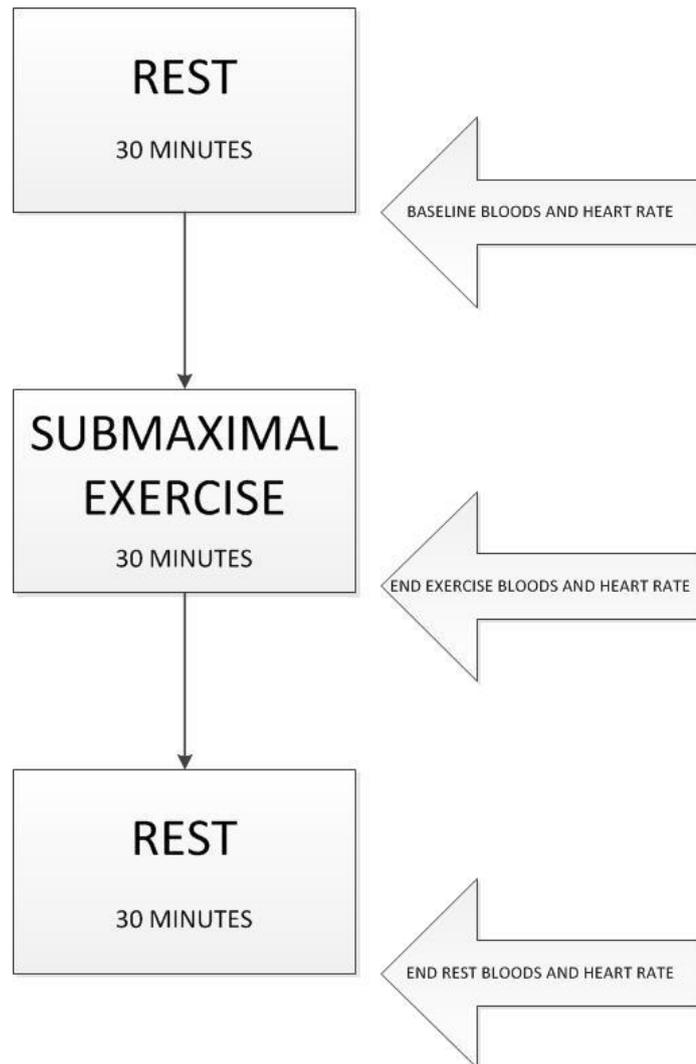
Figure 6-1: BDNF Exercise Testing Data Collection Process

6.3.6 Laboratory processing:

Samples were stored on ice for the duration of the testing session (90 minutes) and for transportation to the processing laboratory (20 minute journey). On arrival at the

laboratory the samples were centrifuged for 30 minutes (1560g's) at 3000rpm in a refrigerated centrifuge pre-chilled to 4°C. The supernatant serum/plasma was then transferred to 2ml Corning cryotubes and placed into a -85°C Sorvall freezer within 4 hours of collection for later analysis of the serum concentration of BDNF and plasma concentration of lactate. All samples were analysed within six months of storage. Immediately prior to analysis the serum samples were thawed in a 37°C water bath.

BDNF

The serum samples were pre-diluted 1:500 in the kitset diluent. Microplate incubation was undertaken using a Microplate shaker. at the recommended temperatures and time. The optical density of the microplate wells were determined at 450nm in a Thermo Scientific Multiskan FC microplate reader. BDNF levels were calculated from the linear regression graph of the standards using the formula (y=cx+m; where c = constant, m= slope and x = test sample value) for the standard curve of each test batch, corrected for the 1:500 dilution, and the BDNF value expressed in ng/mL.

Lactate

Plasma concentrations of lactate were assessed by lactate enzymatic oxidation using a Roche Cobas® Modular P Analyser and the Roche Lactate kit (Cat. No. 11822837). Samples and reagents were used according to the manufacturer's instructions and the analyser calibrated using the Roche calibrator for automatic systems (Cat. No. 10759350). The plasma lactate levels were automatically calculated and reported in mmol/L.

6.3.7 Data Analysis

Data analysis was performed using SPSS software package (version 19) [286]. Inspection of raw data and testing for the normality of the distribution of the dependent variables using the Shapiro-Wilks Test was undertaken to evaluate the distribution of all continuous variables. No variables were found to be significantly non-normal. Data analysis involved descriptive analysis of group characteristics, comparison of within and between group interactions and test-retest reliability of measures. For all statistical analyses a significance level of $p<.05$ was set. Descriptive analysis of group characteristics and physical function included information on the mean, standard deviation, minimum and maximum of continuous data. Descriptive analysis of the stroke group characteristics also included stroke related variables.

Statistical analysis of between and within group differences were analysed using two-way mixed Repeated-measures analysis of variance (rANOVA). rANOVA enables the analysis of variance when the same measurement is made several times on each participant in two separate groups; testing both the between-subject factors and the within-subject factors and elucidating any interactions between factors. rANOVA was used to evaluate the impact of Measurement Point (Baseline, Exercise, Rest), as a within-subject factor, and Group (Control, Stroke), as a between subject factor, on Heart Rate, Lactate and BDNF levels. Type IV rANOVA were utilised to account for any missing data points, with post-hoc testing using Bonferroni's correction to compare any differences among specific means.

Inter -session test-retest reliability of Heart Rate, lactate and BDNF measures were evaluated using two-tailed paired t-tests, intra-class correlation coefficients (ICC), typical error (TE) and the standard error of the measure (SEM). The two-tailed paired t-tests determines whether the group mean changed over time (where $p>0.05$). A two-way random, absolute agreement ICC provides an assessment of the reproducibility of the rank order of the participants on a given measure, while the 95% confidence interval indicates the likely range of the ICC in the true population [287]. ICC values were interpreted based on Landis and Koch standards for strength of agreement; 0 – 0.2 (poor), 0.2 – 0.4 (fair), 0.4 – 0.6 (moderate), 0.6 – 0.8 (good) and 0.8 – 1.0 (excellent) [288]. TE is a measure of within-subject variability encapsulating both biological variability and technical error inherent in the measure. It provides an indication of the precision of the measure which is not influenced by the heterogeneity of the sample [289]. TE was calculated using the equation

$$\text{TE} = \left(\frac{Sdiff}{\sqrt{2}}\right)$$

where S_{diff} is the standard deviation of the individual difference scores between measurement 1 and measurement 2 [281]. To enable comparison of within-subject variability across measures, the coefficient of variation of TE was also calculated. SEM is the standard error in an observed score and is calculated using the equation

$$SEM = SD * \sqrt{1 - r_{xx}}$$

where SD is the standard deviation of measurement 1 and r_{xx} is the coefficient of reliability of measurement 1 and measurement 2, in this case the ICC value. SEM is usually presented as a raw value, however it can be referenced to the mean of measurement 1 (also known as the CV of SEM) to enable comparison between measures, studies and groups with differing ranges of scores, such as between healthy participants and those with stroke.

6.3.8 Data Screening

Following data collection and laboratory processing, data was screened. Visual checking of raw data revealed partial errors in laboratory processing of three participants; one healthy participant and one stroke participant had a single lactate measurement value missing (Case 18, Case 27) and one stroke participant had three BDNF measurements missing due to errors in laboratory processing (Case 31).

Cross checking of data entered into SPSS (version 19) against raw data was carried out to ensure the accuracy of data entry. Data from twenty per cent of the total sample (three stroke participants and four control participants) were randomly selected for cross checking. No inconsistencies were identified. Visual checking of the range of scores and consideration of the plausibility of the mean and standard deviation for each variable revealed no inconsistencies, except for one control participant who had resting lactate measures well above normal resting values (Case 29). These data were consequently excluded from analysis of lactate measures.

6.4 Results

6.4.1 Recruitment and Retention

Twenty two healthy participants volunteered for the study. Two healthy participants withdrew from the study *after* the first testing session; one due to an unrelated medical condition and one due to personal commitments. Of the 30 people with stroke who volunteered for the study, 20 met the inclusion criteria. Five stroke participants withdrew from the study *prior* to the first testing session; two due to unrelated medical issues and three due to personal commitments which coincided with the testing schedule. Data collection was completed from January to March 2010

The data for two stroke participants were removed from the reliability analysis because they exercised significantly prior to a testing session; one stroke participant became lost on campus and walked for more than 20 minutes trying to find the laboratory, a second stroke participant reported that he was so surprised by his capacity to exercise that after the first testing session he borrowed an exercycle and began exercising every day between the first and second testing sessions. There were no differences in statistical analysis outcome with and without excluded cases. Recruitment and retention is illustrated below in Figure 6-2

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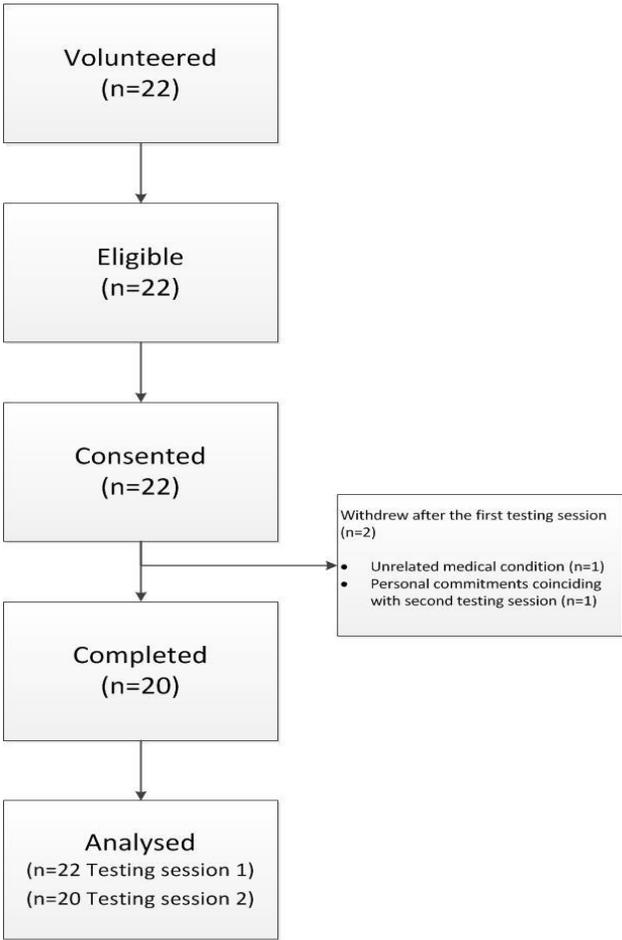
Healthy Participants   **Stroke Participants**
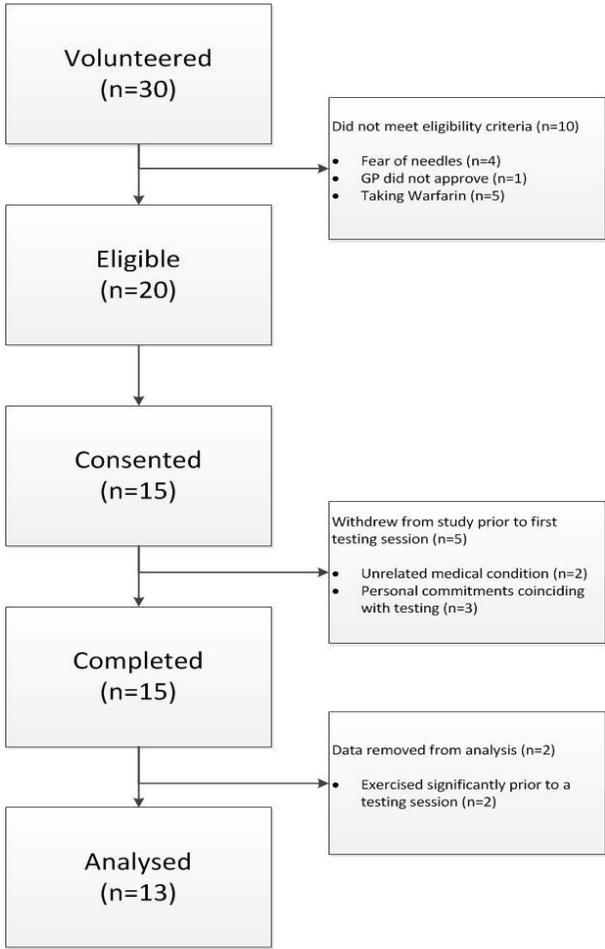
Figure 6-2 BDNF Recruitment and Retention of Healthy and Stroke Participants

6.4.2 Descriptive Analysis

Sample Characteristics

The mean age of the stroke sample was 65.1 years (sd=13.0, range 33-81), with twelve male (80%) and three female (20%) participants. The mean age of the control sample was 55.6 years (sd=13.8, range 33-84), with eleven male (50%) and eleven female (50%) participants. Those in the stroke group were on average 10 years older than the control group (p = 0.04). Although there are more males than females in the stroke group this was not statistically significantly different to the equal ratio of males to females in the control group (p=0.13). Six participants in the stroke group had right hemiplegia (40%) and nine participants had left hemiplegia (60%). The mean time since onset of stroke was 99.9 months (range 31-219).

More people in the stroke group took prescription medications (92%) than the control group (30%). Medications included ß-blockers (Control=10%, Stroke=15%), Anti-hypertensive (Control=5%, Stroke=92%), Low-dose anticoagulants (Control= 10%, Stroke =92%), CNS medications (Control=5%, Stroke =38%), Diabetic medications (Control=5%, Stroke =8%) and other medications (Control=20%, Stroke=46%).

Exercise Task Characteristics

All participants in the control group completed the exercise task using a standard cycle ergometer. One participant in the stroke group used a recumbent cycle and one participant a floor mounted pedal exerciser and chair to complete the cycle task. Two stroke participants required manual assistance to maintain their affected foot on the cycle ergometer during the exercise task.

All participants in both groups worked at or above the specified RPE throughout the task (range, Control=12-15, Stroke=13-16). There was a trend toward a higher RPE at end exercise in the stroke group compared to the control group (Control μ=13.45, Stroke μ=14.00, p=0.08). The mean percentage of age predicted maximum heart rate (%APMHR) achieved during the cycle task was 74% in the stroke group (range = 60%-93%) and 79% in the control group (range= 65%-92%), there was no statistically significant difference in %APMHR achieved during the cycle task between the groups (p=0.257). Three participants in the stroke group and five participants in the control group exceeded the recommended 85% APMHR for submaximal exercise at the end of the cycle ergometry task. Five participants in the control group (25%) and three participant in the stroke

group (23%) did not attain a blood lactate concentration of 4.0 mmol/L or greater during the cycle task.

Heart Rate

The results of the Heart Rate measures taken at Baseline, the end of the Exercise period and at the end of the Rest period are shown in Table 6-1 for the control group and Table 6-2 for the stroke group. Visual comparison of the range, mean and standard deviation suggests that Heart Rate was similar between groups and across testing sessions. Heart rate elevated in response to exercise and returned to near baseline levels after 30 minutes rest in both groups.

Table 6-1 Heart Rate- Control Group

| | Testing Session 1 | | | Testing Session 2 | | |
	Baseline	Exercise	Rest	Baseline	Exercise	Rest
N	22	22	22	20	20	20
Mean	67.00	128.82	75.68	64.70	127.85	72.55
SD	9.48	15.80	10.11	8.45	19.95	10.15
Range	48 - 80	99 - 158	57 - 91	48 - 76	92 - 162	51 - 95

Note: N= Number of participants, SD=Standard Deviation

Table 6-2 Heart Rate – Stroke Group

| | Testing Session 1 | | | Testing Session 2 | | |
	Baseline	Exercise	Rest	Baseline	Exercise	Rest
N	13	13	13	13	13	13
Mean	72.33	116.77	78.31	69.62	116.46	78.85
SD	10.73	18.53	10.28	9.09	22.56	12.44
Range	52 - 87	93 - 155	57 - 91	52 - 82	87 - 157	57 - 106

Note: N= Number of participants, SD=Standard Deviation

Lactate

The results of the Lactate measures taken at Baseline, Exercise and Rest are shown in Table 6-3 for the control group and Table 6-4 for the stroke group. Visual comparison of the range, mean and standard deviation suggests that Lactate measures were similar across the two testing sessions and between the groups. Lactate elevated in response to exercise and returned toward baseline levels during subsequent rest in both groups.

Table 6-3 Lactate – Control Group

	Testing Session 1			Testing Session 2		
	Baseline	Exercise	Rest	Baseline	Exercise	Rest
N	21	21	21	19	19	19
Mean	1.16	3.98	2.23	1.36	4.26	2.28
SD	0.30	2.10	0.75	0.41	1.98	0.57
Range	0.77-1.89	1.10-8.02	1.16-3.90	0.68-2.19	1.02-7.93	1.04-3.76

Note: N= Number of participants, SD=Standard Deviation

Table 6-4 Lactate – Stroke Group

	Testing Session 1			Testing Session 2		
	Baseline	Exercise	Rest	Baseline	Exercise	Rest
N	12	13	12	12	13	12
Mean	1.27	4.12	2.44	1.61	3.94	2.62
SD	0.43	1.44	0.63	0.47	1.29	0.66
Range	0.64 - 2.07	1.11 - 6.41	1.38 - 3.48	0.81 - 2.77	1.39 - 6.06	1.82 - 3.74

Note: N= Number of participants, SD=Standard Deviation

BDNF

The results of the BDNF measures taken at Baseline, Exercise and Rest are shown in Table 6-5 for the control group and Table 6-6 for the stroke group. Visual comparison of the range, mean and standard deviation suggests that BDNF measures were similar between the groups. However, the mean of scores for Exercise and Rest appear lower in the second testing session (End Exercise Control: μ=33.76, SD=12.93 Stroke μ=29.78, SD=14.70) than the first (End Exercise Control: μ=41.07, SD=13.92 Stroke μ=39.20, SD=13.22) in both groups. In both groups BDNF increased in response to exercise and returned to below baseline levels during subsequent rest.

Table 6-5 BDNF – Control Group

	Testing Session 1			Testing Session 2		
	Baseline	Exercise	Rest	Baseline	Exercise	Rest
N	22	22	22	20	20	20
Mean	33.30	41.07	31.58	28.47	33.76	24.37
SD	10.21	13.92	10.93	10.44	12.93	10.48
Range	17.68 - 49.18	20.49 - 71.60	11.95 - 49.18	13.36 - 48.07	14.90 - 56.88	9.45 - 49.98

Note: N= Number of participants, SD=Standard Deviation

Table 6-6 BDNF – Stroke Group

	Testing Session 1			Testing Session 2		
	Baseline	Exercise	Rest	Baseline	Exercise	Rest
N	13	13	12	13	13	13
Mean	36.60	39.20	29.05	29.89	29.78	26.24
SD	13.01	13.22	12.15	12.00	14.70	14.36
Range	17.15 - 53.35	21.27 - 61.44	14.34 - 48.82	16.19 - 61.64	6.27 - 57.95	4.57 - 53.43

Note: N= Number of participants, SD=Standard Deviation

6.4.3 Inferential Analysis

rANOVA's were used to analyse the effect of measurement point and group, and the effect of interaction between measurement point and group on each of the measures (Heart Rate, Lactate and BDNF) taken during testing session 1.

Heart Rate

Mauchleys test indicated that the assumption of sphericity had been violated ($X^2(2)$ = 41.83) therefore the Greenhouse-Geisser correction was used. A large main effect for measurement point was found; where Heart Rate differed significantly between measurement points ($F(1.16, 38.146) = 278.69$, r= .894 P < .001). Post hoc tests using the Bonferroni correction revealed that Heart Rate increased significantly (P<0.001) from Baseline to the end of the Exercise period (68.94 ± 10.13 vs. 124.34 ± 17.62, respectively) and decreased significantly (P<0.001) from the end of the Exercise period to the end of the Rest period (124.34 ± 17.62 vs. 76.66± 10.11, respectively).

There was no main effect for Group; where Heart Rate did not differ significantly between the groups ($F(1,33)=2711.81$, r=.005, P=.688). There was a small but statistically significant interaction effect between Group and Measurement Point ($F(1.56, 38.16)=7.29$, r=.181 P=.008). This indicated that the change in Heart Rate between measurement points differed between the stroke group and the control group. To analyse this interaction post-hoc tests using the Bonferroni correction were applied. Post hoc tests revealed significant differences between the groups from Baseline to Exercise (P=0.007) and from Exercise to Rest (P=0.014), where the control group had a greater increase in Heart Rate from Baseline to Exercise and a greater decrease from Exercise to Rest than the stroke group. These differences are illustrated in Figure 6-3 which shows the mean and standard error of the mean for Heart Rate in both the stroke and control groups at each measurement point during testing session 1.
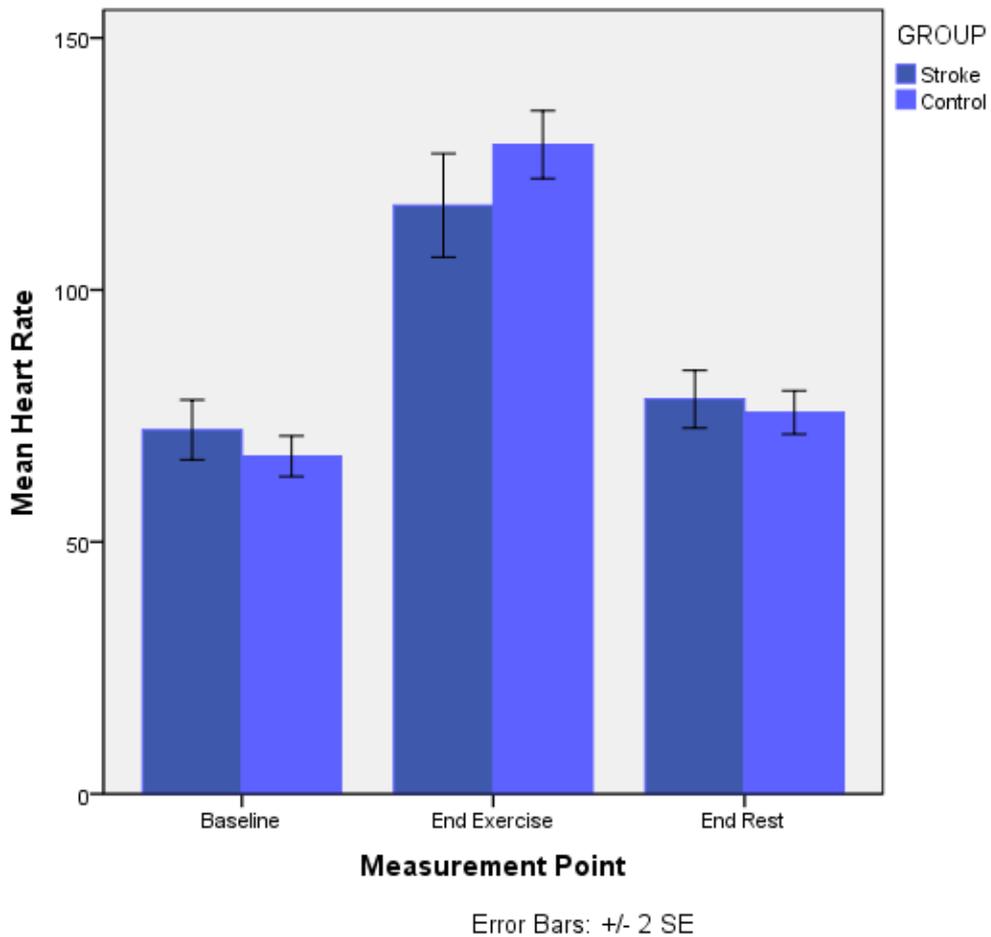
Figure 6-3 Mean Heart Rate by Measurement Point and Group

Lactate

Mauchleys test indicated that the assumption of sphericity had been violated ($X^2(2) =$ 35.94) therefore the Greenhouse-Geisser correction was used. A large main effect for measurement point was found; where Lactate differed significantly between measurement points ($F(1.14, 30.88) = 57.63$, r= .68 P < .001). Post hoc tests using the Bonferroni correction revealed that Lactate increased significantly (P<0.001) from Baseline to Exercise (1.29 ± .35 vs. 4.10 ± 1.80, respectively) and decreased significantly (P<0.001) from Exercise to Rest (4.10 ± 1.80 vs. 2.34± .69, respectively). There was no main effect for Group; where Lactate did not differ significantly between the groups ($F(1,27)$=.006, r=.000, P=.938). There were no interaction effects between Group and Measurement Point ($F(1.14, 30.88)$=.089, r=.003 P=.801). This indicates that the change in Lactate between measurement points did not differ between the stroke group and the control group. These findings are illustrated in Figure 6-4 which provides a pictorial representation of the mean

and standard error of the mean in Lactate levels in both the stroke and control groups at each measurement point during testing session 1.
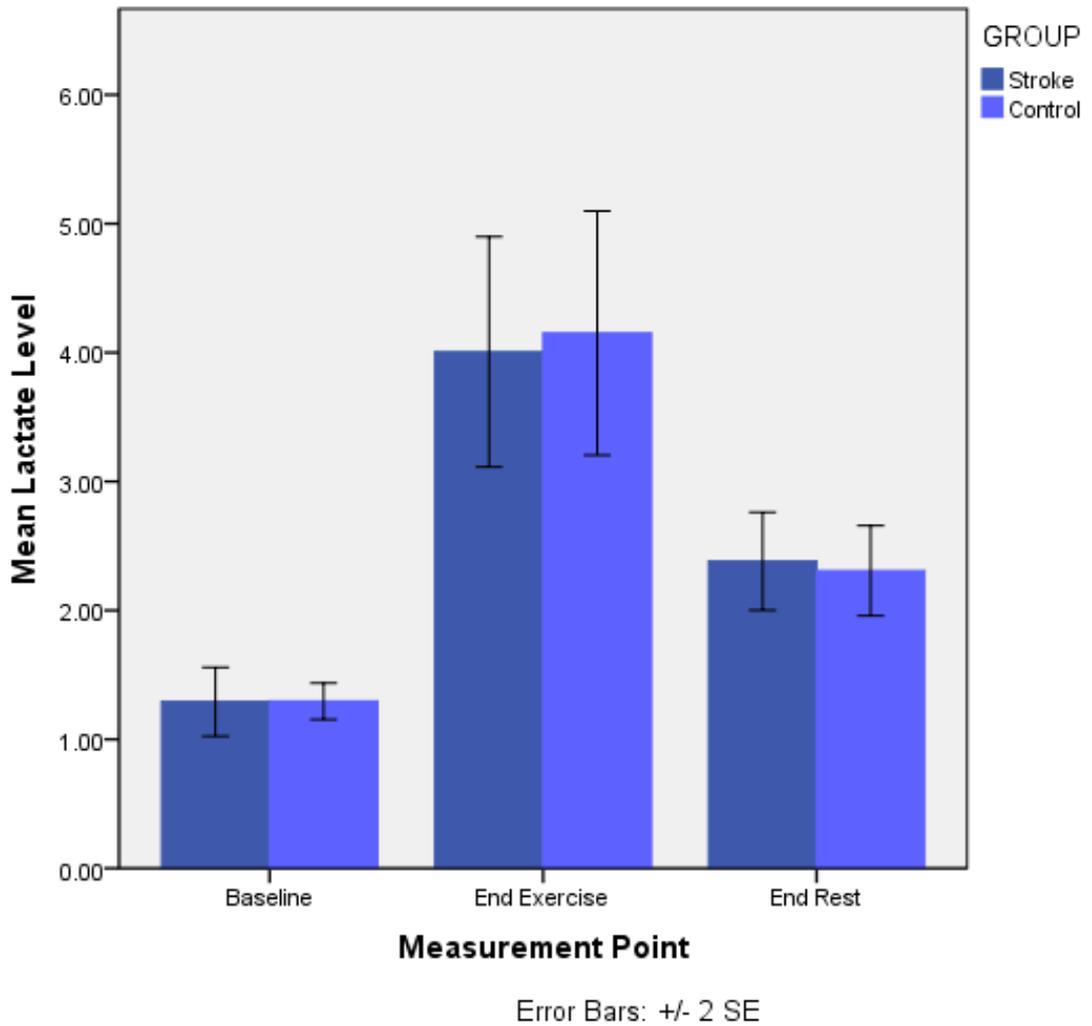
Figure 6-4 Mean Lactate by Measurement Point and Group

BDNF

Mauchleys test indicated that the assumption of sphericity had been met. A large main effect for measurement point was found; where BDNF differed significantly between measurement points ($F(2, 64) = 30.13$, r= .485 P < .001). Post hoc tests using the Bonferroni correction revealed that BDNF increased significantly (P<0.001) from Baseline to Exercise (34.33 ± 11.37 vs. 40.68 ± 13.58, respectively) and decreased significantly (P<0.001) from Exercise to Rest (40.68 ± 13.58 vs. 30.69± 11.26, respectively). There was no main effect for Group; where BDNF did not differ significantly between the groups ($F(1,32)=291.33$, r=.000, P=.953).

There were no significant interaction effects between Group and Measurement Point (F(2, 64)=2.29, r=.181 P=.11). This indicates that the change in BDNF between measurement points did not differ significantly between the stroke group and the control group. These findings are illustrated in Figure 6-5 which provides a pictorial representation of the mean and standard error of the mean in BDNF levels in both the stroke and control groups at each measurement point during testing session 1.

Error Bars: +/- 2 SE
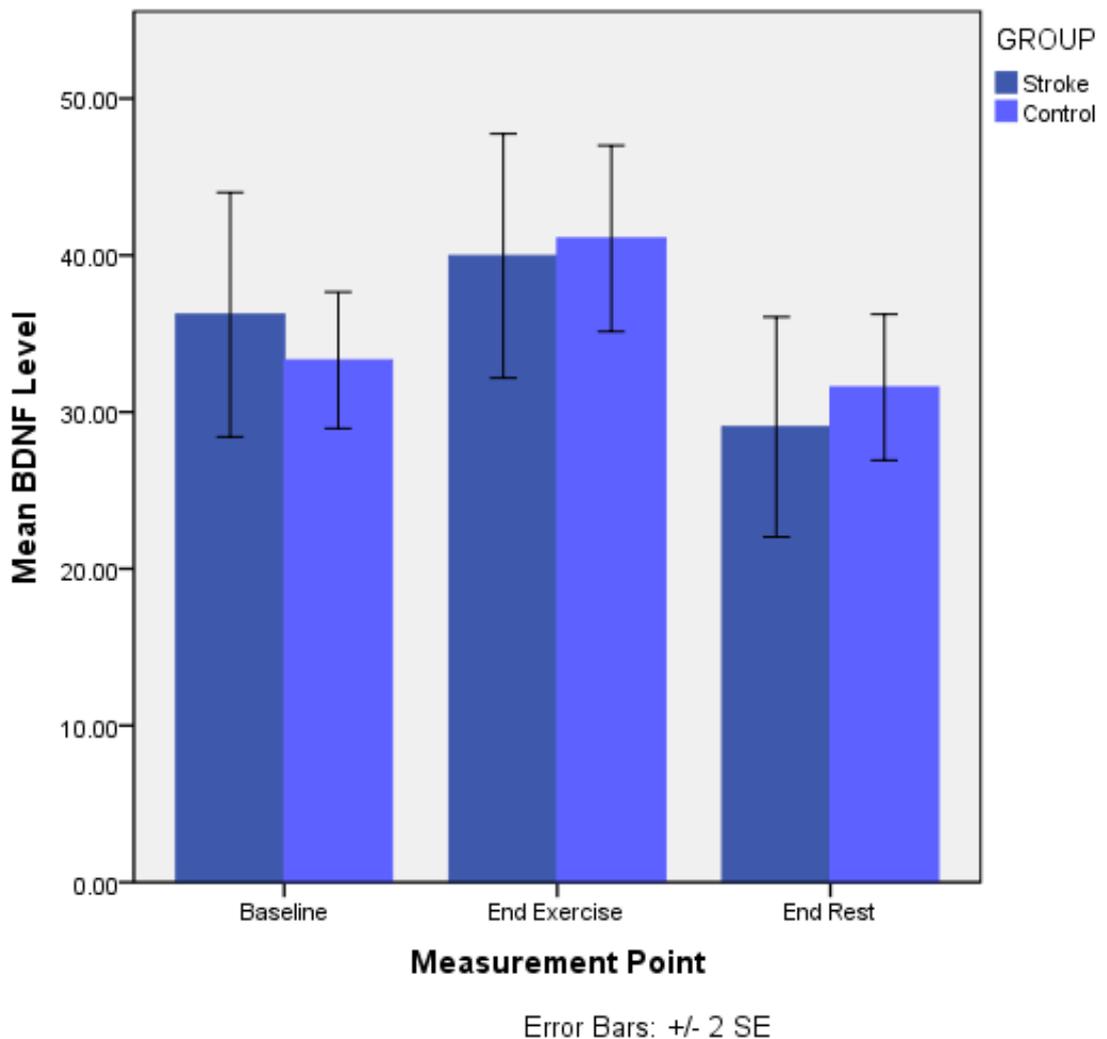
Figure 6-5 Mean BDNF by Measurement Point and Group

6.4.4 Reliability Analysis

The following section presents the results of the inter-session reliability analysis for Heart Rate, Lactate and BDNF.

Heart Rate

The intra-class correlation coefficients (ICC), ICC 95% confidence interval, TE and SEM for Heart Rate at the three measurement times are presented in Table 6-7

Paired t-tests indicated that there was no absolute systematic bias or learning effect between Testing Session 1 and Testing Session 2; except for the Rest measurement point in the Control group (P=.027), where Heart Rate was on average 2.5% lower in the Testing Session 2.

Table 6-7 Heart Rate Test-retest Reliability

		Control (n=20)	Stroke (n=13)
Baseline	ICC (95% CI)	0.80 (0.61-0.90)	0.80 (0.55-0.92)
	TE (CV)	4.25 (9%)	4.74 (7%)
	SEM (CV)	1.00 (1%)	1.13 (2%)
Exercise	ICC (95% CI)	0.82 (0.65-0.91)	0.89 (0.72-0.96)
	TE (CV)	7.56 (8%)	7.58 (6%)
	SEM (CV)	1.49 (1%)	1.05 (1%)
Rest	ICC (95% CI)	0.80 (0.61-0.90)	0.82 (0.58-0.93)
	TE (CV)	3.82 (7%)	5.23 (7%)
	SEM (CV)	1.07 (1%)	0.97 (1%)

Note: ICC=Intra-class correlation coefficient, TE=Typical Error, SEM=Standard error of the measure, CV=Coefficient of variation

The ICC measures were excellent (≥.80) across all measurement points, for both groups, with correspondingly high 95% confidence intervals. The TE was also similar between the groups, and across the measurement points, demonstrating low within-subject variability (CV of TE=6-9%).

In summary, measures of Heart Rate taken at rest, during and after submaximal exercise demonstrate excellent test-retest reliability in people with stroke and control participants.

Lactate

The ICC's, ICC 95% confidence interval, TE and SEM for Lactate at Baseline, Exercise and Rest are presented in Table 6-8.

Table 6-8 Lactate Test-retest Reliability

		Control (n=19)	Stroke (n=12)
Baseline	ICC (95% CI)	0.54 (0.20-0.76)	0.42 (0.08-0.74)
	TE (CV)	0.25 (19%)	0.36 (28%)
	SEM (CV)	0.08 (6%)	0.15 (12%)
Exercise	ICC (95% CI)	0.85 (0.69-0.93)	0.28 (-0.20-0.65)
	TE (CV)	0.84 (20%)	1.18 (29%)
	SEM (CV)	0.16 (4%)	0.68 (17%)
Rest	ICC (95% CI)	0.59 (0.26-0.80)	0.62 (0.20-0.84)
	TE (CV)	0.44 (19%)	0.42 (17%)
	SEM (CV)	0.17 (7%)	0.13 (5%)

Note: ICC=Intra-class correlation coefficient, TE=Typical Error, SEM=Standard error of the measure, CV=Coefficient of variation

Neither group's mean difference between Testing Session 1 and Testing Session 2 was statistically different at any measurement point, suggesting that there was no absolute systematic bias between testing at Testing Session 1 and Testing Session 2; except for the Baseline Measurement point in the stroke group (p=0.037), where Lactate was on average 27% higher in the second testing session.

The ICC's varied between the groups and across the measurement time points. The ICC was moderate for the control group at Baseline (ICC=0.54) and Exercise (ICC=0.59) and excellent at exercise (ICC=0.85). In contrast; the ICC's were moderate to good for the stroke group at Baseline (ICC=0.42) and Rest (ICC=0.62) and fair at Exercise (ICC=0.28).

The TE was modest, and both absolute and relative TE were larger in the stroke at Baseline and Exercise.

In summary, measures of Lactate taken during submaximal exercise demonstrate excellent test-retest reliability in the control group and fair test-retest reliability in the stroke, and only moderate to good test-retest reliability before and after submaximal exercise in both Stroke and Control groups.

BDNF

There was no statistically significant difference between Testing Session 1 and Testing Session 2 for either group at any measurement point. However, the variance of these measures was large and the mean difference between Testing Session 1 and Testing Session 2 is negative in both groups at each measurement point, indicating that there may be a systematic bias which is not identified on statistical analysis, where the BDNF response is smaller in the second testing session.

The ICC, ICC 95% confidence interval, TE and SEM for BDNF at Baseline, Exercise and Rest are presented in Table 6-9..

Table 6-9 BDNF Test-retest Reliability

		Control (n=19)	Stroke (n=13)
Baseline	ICC (95% CI)	0.44 (0.08-0.69)	0.42 (-0.04-0.74)
	TE (CV)	7.93 (24%)	9.79 (27%)
	SEM (CV)	3.44 (10%)	4.58 (13%)
Exercise	ICC (95% CI)	0.45 (0.10-0.70)	0.21 (-0.27-0.61)
	TE (CV)	9.61 (23%)	12.55 (32%)
	SEM (CV)	4.58 (11%)	7.16 (18%)
Rest	ICC (95% CI)	0.26 (-0.12-0.58)	0.17 (-0.34-0.59)
	TE (CV)	9.17 (29%)	12.59 (43%)
	SEM (CV)	5.36 (17%)	7.14 (25%)

Note: ICC=Intra-class correlation coefficient, TE=Typical Error, SEM=Standard error of the measure, CV=Coefficient of variation

The ICC's varied between the groups and across the measurement points. The ICC was moderate for the control group (ICC=0.44) and the stroke group (ICC=0.42) at Baseline. However the ICC's of the stroke group were fair at Exercise (ICC=0.21) and poor at Rest (ICC=0.17); compared to the control group which were moderate (ICC=0.45) and fair (ICC=0.26) respectively. The TE's were moderate, with larger absolute and relative values in the stroke group than the control group, suggesting greater within subject variability in the stroke group.

6.5 Discussion

The aim of this study was to evaluate the inter-session reliability of blood serum derived measures of BDNF before, during and after a bout of sub-maximal exercise in people with stroke and healthy participants. A secondary aim of the study was to identify any differences between the groups in the release of BDNF in response to sub-maximal exercise and uptake during subsequent rest. The results of the study indicate that people with stroke have a comparable BDNF response to healthy control participants during sub-maximal exercise and subsequent rest. Measures of serum BDNF demonstrated poor to moderate test-retest reliability in both the control and stroke groups; with moderate within-subject variability. This section compares the results of the current study with other studies in healthy participants and people with chronic disability, and discusses the potential influence of the sample and method on the study findings.

6.5.1 Basal BDNF Levels

As previously identified in Section 5.5 the raw values for serum BDNF vary widely in the research literature, with group averages for basal levels of serum BDNF in healthy participants published between 2003 and 2012 ranging from 0.56 ng/mL [290] to 30.9 ng/mL [263]. The average basal level of serum BDNF in the current study were 33.3 ng/mL in the control group and 36.6 ng/mL in the stroke group. These levels are slightly above the range of values previously reported in the literature. The SD's in the current study were large and represent considerable between subject variability in serum BDNF values. Inter-subject variability is acknowledged in the literature, with sample CV's ranging from 23-67% [260, 261, 263, 266, 268, 291-294]. The sample CV's for basal BDNF in the current study were comparable between the groups (Sample CV, Control=31%, Stroke=36%) and within the range of previously reported results.

The slightly elevated basal BDNF levels in the current study, in comparison to previous studies, may in part be explained by ELISA kit differences with some kits, including the ChemiKine™ Millipore kit, yielding higher BDNF values than others [295]. The methods used for collection, storage and laboratory processing can also influence the level of BDNF found in a sample [279, 294]. Whilst these processes were tightly controlled and based on recommendations from previous literature [256, 279] and the ELISA kit manufacturers, differences in processing may have influenced the BDNF values; particularly the length of time the samples were kept on ice prior to processing in the laboratory [294].

Inferential analysis revealed no statistically significant difference in basal serum BDNF levels between the groups. This finding is in contrast to research in other neurological disorders such as Alzheimer's Dementia, Parkinson's Disease and Multiple Sclerosis, where studies generally report lower basal serum BDNF levels in people with these neurological pathologies in comparison to healthy controls [256, 296]. However, this appears to be related to disease progression [268, 296] and it is important to note stroke is usually a single event pathology. BDNF level may be expected to have reached a steady state in people who are more than six months post-stroke.

The two groups were different in terms of gender balance and age; the control group were younger and had more females than the stroke group. Recent large studies investigating basal serum BDNF levels in healthy participants suggest that BDNF levels may change with age and may be different between the sexes, although results are conflicting. Elfving and colleagues demonstrated that serum BDNF levels increase with increasing age in a working age population of men and women [293]. This finding was confirmed by Jung and colleagues in a large group of men aged between 20-76 years [297]. However, other research studies which have included a wider age range and gender balanced sample indicate that BDNF levels decrease with increasing age in older women but remain stable in older men, this difference may relate to menopause in women [292, 298]. Collectively it is suggested that basal serum BDNF levels increase with age through middle age and then decrease into older adulthood, and that this effect is greater or only present in women. The influence of the age-gender interaction on basal BDNF levels in the current study therefore may have differed between the groups. Based on the greater number of younger, presumably pre-menopausal, females in the control group it might be expected that the average BDNF level would be greater in the control group than the stroke group. This was not the case.

Study participants volunteered to take part, which may have introduced a significant selection bias in both the control and stroke groups; the samples likely represent people who are relatively healthy and physically active compared to their source populations. The influence of lifestyle, cardiovascular and metabolic factors on BDNF levels requires consideration. It may be assumed that the stroke group had more concomitant medical conditions, greater metabolic risk factors, lower cardiovascular fitness, undertook less regular physical activity, and had higher body mass than the control group; although these variables were not explicitly measured as part of the study. Basal levels of serum BDNF have been shown to be influenced by; concomitant medical conditions such as Type II Diabetes Mellitus [299] and Depression [298, 300, 301], metabolic risk factors such as elevated BMI [302], disturbed blood lipid profiles [303], and food and alcohol intake [256, 304]. In the current study medication data indicates that more people in the stroke group took medications for cardiovascular disease and depression; suggesting that the influence of these diseases on BDNF levels may have been greater in the stroke group. Some medications are also known to specifically influence BDNF levels, including anti-platelet therapies and antidepressants [300, 304]; medication effects are more likely to have occurred in the stroke group. Reduced cardiovascular fitness and physical activity levels have also recently been shown to influence basal BDNF levels, where those with better cardiovascular fitness and higher levels of physical activity have lower levels of basal BDNF [280, 297, 305-307]. This might be expected to result in higher BDNF levels in the control group than the stroke group; this was not the case.

In summary, methodological and sample differences may explain the slight elevation in basal serum BDNF levels found in the current study in comparison to previous research. There was no statistically significant difference in serum BDNF levels at rest between people with stroke and healthy controls. However, group differences may have been obscured by the influence of covariates, such as lifestyle and health factors, which were not accounted for in the current study.

6.5.2 BDNF Levels in Response to Exercise

As indicated by both the descriptive and interferential analyses BDNF increased from Baseline to the end of the Exercise period and decreased from Exercise to Rest in both the control group and the stroke group in testing session one. This finding is in keeping with previous studies [260, 261, 263, 264, 266-268, 305, 308-310]. Change in BDNF levels in response to exercise are thought to illustrate BDNF's pivotal role in neural plasticity in

response to exercise and physical activity [256], with changes in serum BDNF levels reflecting brain tissue BDNF levels [259].

Studies which investigate BDNF expression in response to sub-maximal exercise in healthy people report increases from baseline of 0-25% [260, 261, 263, 264, 266-268, 305, 308-310], with the magnitude of the response likely related to the duration and intensity of the exercise [260, 261, 266, 291, 308, 310]. Similar responses to sub-maximal exercise have been demonstrated in people with chronic neurological pathology such as spinal cord injury and multiple sclerosis [267, 268, 311]. The average increase from baseline in response to exercise testing session 1 in the current study was 23% in the control group and 7% in the stroke group, which is within the range of previously reported results for moderate intensity exercise. The serum BDNF returned to below baseline levels by the end of the 30 minutes post-exercise rest period in both groups. The relative decrease from the baseline level at end of rest in testing session 1 was 5% in the control group and 21% in the stroke group. It is worth noting that in the second testing session the average change from baseline in response to exercise was a decrease of 4% in stroke group, with a 12% decrease from the baseline level at the end of the post-exercise rest period, although the reliability testing indicated no statistically significant difference between the two testing sessions in either group at any measurement point. This emphasises that the results of the inferential analysis are likely underpowered given the findings of the reliability testing.

The calculated magnitude of change in response to exercise and subsequent rest may have been influenced by changes in blood volume in response to exercise. A review by Kargotich and colleagues indicates that haemoconcentration occurs in response to moderate intensity cycle ergometry and haemodilution occurs during subsequent rest [312]. This may artificially inflate the serum BDNF levels during exercise and reduce levels in the post-exercise rest period. However, similar responses to submaximal exercise have been reported irrespective of correction for blood volume changes.

There was considerable between subject variation in BDNF response to submaximal exercise. A number of researchers investigating BDNF in response to exercise have reported 'outliers' in their samples and consequently have elected to exclude these participants from their analyses [258, 268, 313]. It may be questioned whether these participants represent true outliers or reflect the considerable inter-subject variability in BDNF values.

Interferential analysis revealed that the change in BDNF in response to exercise and subsequent rest did not differ significantly between the groups, indicating that people

with stroke and healthy controls were not different in their expression and uptake of BDNF in response to exercise and rest. The results of studies in people with neurological pathology and sedentary lifestyles present somewhat contradictory results for comparison. Investigating people with Multiple Sclerosis, Castellano found differences between people with MS and healthy controls in the rate of uptake of BDNF during rest subsequent to 30 minutes of sub-maximal cycle ergometry [267]. They did not measure BDNF at the end of the exercise period, so it is unclear if there were differences in the expression of BDNF between the groups or not. In contrast, Gold found no difference in BDNF expression in response to 30 minutes of sub-maximal cycle ergometry or in the uptake of BDNF during a subsequent 30 minute rest period when comparing people with MS to healthy participants [268]. Nofuji has recently conducted a study comparing physically sedentary and active healthy participants in their response to exercise of maximal, sub-maximal and low intensity. They found that there was a difference between the groups with respect to the uptake of BDNF during a 60 minute rest period following maximal exercise, where the active group dropped below the baseline level of BDNF whilst the sedentary group only reached baseline levels [305]. This effect was not seen in moderate or low intensity exercise, suggesting that group differences between healthy participants and people with neurological pathology or sedentary lifestyles may only be apparent during maximal exercise testing.

In addition to those factors described in Section 6.5.1 which influence basal BDNF levels, a number of factors may have specifically influenced the findings with respect to expression and uptake of BDNF in response to exercise. The variant of the human BDNF gene Val66Met, which occurs in 20-30% of the population, is thought to result in decreased expression of BDNF in response to activity. Participants who have this gene mutation are likely to have lower BDNF levels in response to exercise [256] although not lower basal BDNF levels [279]. The proportions of people with the Val66Met polymorphism may have differed between the groups and thereby influence the results in respect to exercise. Factors related to the physiological demands of the exercise task may also have differed between the groups and are discussed below in Section 6.5.3.

6.5.3 Reliability Findings

Heart Rate

The inter-session reliability of Heart Rate measures in both control and stroke participants was excellent across all measurement points, indicating that baseline heart rate, heart rate response to sub-maximal exercise at a specified RPE and heart rate during

recovery from submaximal exercise are highly reliable in both people with stroke and healthy participants. The within subject variability was also similar between the groups, and across the measurement points, demonstrating low within-subject variability. These findings are in keeping with previous studies investigating the reliability of submaximal and maximal exercise testing in people with stroke [40, 314-316].

Previous researchers have identified the effect of ß-blockers on sub-maximal and maximal exercise responses in people with stroke. It has been noted that ß-blockers may blunt heart rate response and increase ratings of perceived exertion during submaximal exercise, where large increases in work can result in very small changes in heart rate [316, 317]. However, this is not expected to have resulted in a marked difference between the groups as both groups had two participants taking ß-blockers. However it may have inadvertently enhanced the inter-session reliability of heart rate in the exercise period slightly. Although this might be expected to have improved ICC and TE values at exercise in comparison to other measurement points, which was not the case.

Lactate

The inter-session reliability and within subject variability of lactate was similar between the groups at baseline and end rest, indicating that baseline lactate, and lactate after recovery from submaximal exercise have moderate to good reliability in both people with stroke and healthy participants. No studies were identified which evaluated inter-session reliability of lactate measures at rest, although there is strong evidence for excellent inter-session reliability on the same blood sample [318, 319]; suggesting that reduced test-retest reliability of basal blood lactate measures relates to biological variability rather than measurement error. This is supported by research indicating considerable within-subject variation in lactate measures [320] and by the level of within-subject variability seen in the current study at rest.

Lactate levels taken at the end of exercise had excellent reliability for the control group, but only fair for the stroke group. Previous research investigating the reliability of lactate measures in healthy trained adults have also identified good to excellent reliability [321, 322]. In addition studies of rating of perceived exertion at different lactate levels during exercise have demonstrated excellent reproducibility in trained athletes and healthy adults [323, 324]. The poor reliability of lactate at the end of the exercise period in the stroke group may be partially explained by the level of within subject variability of the stroke group, which was greater than the control group. No studies were identified which investigated the within subject variability or reliability of lactate measures in people with

low aerobic capacity, cardiovascular or neurological pathology. The poor inter-session reliability and moderate within subject variability in lactate at end exercise in the stroke group may be due to differences in the physiological response to exercise in people with stroke.

People with stroke have markedly reduced aerobic exercise capacity compared to matched controls, and many changes which may influence physiological response to exercise including; muscle atrophy, fibre type changes, capillary and mitochondrial density changes, voluntary activation deficits, deconditioning and concomitant cardiovascular disease [316, 325]. Whilst none of these factors are likely to change in the seven days between test and re-test in a chronic stroke population, they may introduce greater within subject variability. Alternatively, the novelty of the cycle ergometry task in people with stroke may have altered the participants approach to exercise between time 1 and time 2, however there was no evidence of a systematic bias in either heart rate or lactate response to exercise, suggesting a comparable level of physical activity between testing sessions.

BDNF

Whilst a relatively new field of scientific investigation; BDNF measures have recently been used extensively in research in healthy populations and in people with neurological pathologies. The current study is the first to describe the reliability of BDNF measures. The inter-session reliability of BDNF measures were fair to moderate in the control group and poor to good in the stroke group.

The modest reliability of BDNF measures may be explained by considering the source of the substantial variance in the measure. ICC's are influenced by both the between-subject variability and within subject variability of the measure. Greater between subject variability will increase the ICC value, whilst greater within subject variability will decrease it. The sample heterogeneity in BDNF measures, as above should therefore have elevated the ICC value. The within subject variability in the current study was moderate, and greater in the stroke participants, which may, in part, explain the lower ICC's in the stroke group. Within-subject variability in BDNF measures have previously been reported by Winter who showed that baseline BDNF levels differed significantly over three testing sessions separated by at least seven days in 30 healthy participants [264]. However, Tang reported no statistically significant difference in three basal samples taken 25 minutes apart in their study of eight active and eight sedentary participants, although they went on

to describe marked fluctuations in two participants across the testing session, indicating that within subject variation was an issue in some participants but not others [263].

The collection, transport and storage of samples are potential sources of within-subject variability, however considerable effort was made to standardise the testing procedure and laboratory processes in the current study. Given Trajkovska's [279] finding that intra-sample variation was 12.0% when tested with the same ELISA kit, and the low levels of intra and inter-assay variability it is likely that much of the within-subject variability in the current study is due to biological variability rather than measurement error. As discussed above recent research has highlighted the number of lifestyle and health co-variables which are likely to influence BDNF. It may be asserted that these co-variables are more likely to play a greater role in people with stroke. Inter-session biological variability may also be introduced by variations in the time of day of testing [294, 326], alterations in time of testing relative to medication consumption [300, 304], and variability in participant's food intake [294] and activity levels prior to testing [256]. Variability in exercise and rest measures may also have been introduced by the cycle task itself; however the level of within subject variability for both heart rate and BDNF was consistent at each measurement point suggesting that this is not likely.

6.5.4 Implications for Future Research

This study provides key information which informs the determination of sample sizes in research trials to ensure that research is sufficiently powered to detect differences between groups. The findings of this study indicate that 205 participants per group would be required to detect a 10% difference in basal BDNF levels between stroke and control samples, assuming a p value of 0.05 and 80% power. This indicates the considerable risk that many recent studies published are underpowered to demonstrate differences in BDNF and highlights the importance of large population based studies in unpacking the influence of co-variants on basal BDNF levels.

Based on the current study approximately 20 participants would be required to detect a 20% change in BDNF levels in response to an intervention in people with stroke. However, the selection of a 20% change in BDNF values is arbitrary. Whilst acute exercise paradigms such as the one undertaken in this study highlight a role for BDNF in response to exercise and studies using animal stroke models [272-275, 277, 278] and in people with val66met polymorphism [257, 269, 270] highlight its role in neural plasticity, little is known about its mechanism. It is not yet clear whether circulating BDNF levels reflect a valid measure of its action in the CNS and therefore it may not be a valid biomarker of neural plasticity

[259]. However, changes in basal BDNF levels in response to some exercise interventions in healthy adults [290] and the relationship between cardiovascular fitness and BDNF suggests that it may be modified in response to exercise rehabilitation interventions [290, 297]. Given that the magnitude of change in serum BDNF levels in response to an exercise intervention is currently unknown in people with stroke there is merit in using the BNDF measure in the proposed pilot study. By including the BDNF measure in the pilot study it should be possible to establish the magnitude of difference and variances estimates and therefore to determine whether the change in BDNF level in response to an exercise intervention is likely to exceed the within and between subject variance of the measure.

This study also provides information in relation to interpreting the individual change in BDNF required to be considered a true change. Based on Hopkins work it is suggested that an individual would need to change by 1.5 to two times the relative within subject variability (CV of TE) to be considered a true change [281]. In this sample, a control participant would need to change their basal BDNF value by +/-36% and a stroke participant by +/-39% to be considered a true change. Whilst this magnitude of change is seen acutely in response to exercise in an individual, it is unclear what magnitude of change might be expected following an exercise rehabilitation intervention.

6.5.5 Limitations

This study is potentially limited by:

- A small sample size; with no previous indication to support the determination of sample size the elected sample size was based on the reliability analysis and the study is consequently underpowered for inferential analysis.
- Failure to control or account for potential covariates such as: usual physical activity, co-morbidities, cardiovascular fitness, val66met polymorphism, medications (beyond Wafarin), diurnal and seasonal variability, and the variable modes of exercise used in the stroke group.
- The use of submaximal exercise; it is possible group differences and greater reliability in measures of BDNF may have been elucidated by higher intensity exercise.
- The use of various modes of submaximal exercise to accommodate differing levels of physical disability in the stroke group.

6.6 Summary

BDNF is an important neurotrophin in neural plasticity and motor learning [256] and has recently received considerable scientific attention in human studies investigating neural plasticity, neurological pathology and psychiatric disorders. However the reliability of BDNF as a biomarker of neural plasticity has not been established in healthy adults or people with stroke. In the current study, a repeated measures cross-sectional design, with 7 days between sessions, was used to evaluate the reliability of expression and uptake of BDNF in response to sub-maximal exercise and subsequent rest in healthy and stroke participants. The main findings of the study indicate that;

- Measures of serum BDNF demonstrated poor to moderate test-retest reliability in both the control and stroke groups.
- The inter-session reliability of BDNF measures were influenced by within subject variability; which may be related to biological variability in BDNF levels in response to lifestyle and health covariates.
- Based on interferential analysis there was no differences in the expression and uptake of BDNF in response to sub-maximal exercise and subsequent rest between healthy and stroke participants.
- It is as yet unknown what magnitude of change in BDNF levels might be expected in response to a rehabilitation intervention in people with stroke.

Chapter 7   Test-retest Reliability of TMS

7.1 Prologue

0 described the validity and reliability of TMS as a biomarker of neural plasticity in response to locomotor rehabilitation and noted that the psychometric property of TMS as a measure of corticomotor excitability in the lower limbs has been described in a very limited way. To date, studies indicate that TMS in the affected lower limb in people with stroke has poor inter-session reliability. There are some indications that reliability may be improved when taken during a functional movement task rather than an isometric contraction in people with stroke. Therefore, this chapter aims to address the intra- and inter-session test-retest reliability of TMS in the soleus muscle in healthy participants and people with stroke during an isometric contraction and during a locomotor task.

7.2 Introduction

The aim of this study was to evaluate the reliability of TMS measures of corticomotor excitability of the soleus muscle during an isometric contraction and during walking in healthy people and people with stroke. It was specifically hypothesised that:

1. Control and stroke groups would demonstrate good to excellent *intra-session* reliability (ICC≥0.6) on measures of corticomotor excitability of the soleus muscle during an *isometric contraction*.
2. The control group would demonstrate good to excellent *inter-session* reliability (ICC≥0.6) on measures of corticomotor excitability of the soleus muscle during an *isometric contraction*
3. The stroke group would demonstrate poor to adequate *inter-session* reliability (ICC≤0.59) on measures of corticomotor excitability of the soleus muscle during an *isometric contraction*.
4. Control and stroke groups would demonstrate good to excellent *inter-session* reliability (ICC≥0.6) on measures of corticomotor excitability of the soleus muscle during a *walking task*.

7.3 Method

7.3.1 Study Setting and Design

This study was undertaken at the Health & Rehabilitation Research Institute of AUT University, Auckland, NZ. The study used a repeated measures experimental design involving measurement of corticomotor excitability of the soleus muscle across two testing sessions separated by seven days. Participants were evaluated during an isometric muscle contraction and during walking on a treadmill.

7.3.2 Sample

A target sample size of 15 participants per group was selected based on advice from a biostatistician to ensure power to establish both test-retest reliability and variance estimates.

Recruitment

Participants were recruited to the study through advertisement in local newspapers, at local Stroke Foundation meetings, via AUT Akoranga campus community and AUT University Physiotherapy Clinic's notice boards. In addition a letter of invitation was sent to those people who had previously consented to be contacted in relation to studies being conducted in the Neurophysiology laboratory at the HRRI. Those potential participants who expressed an interest in the study were sent an information sheet. Face to face provision of the study information was also offered.

Inclusion Criteria

All participants with stroke who met the following inclusion criteria were considered for the study;

- Over the age of 18 years
- A single stroke with a resultant hemiparesis affecting their ability to walk
- 6 months or more since stroke
- With a comfortable gait speed of between 0.05 -1.2 m/s

Potential healthy participants who met the following inclusion criteria were considered for the study;

- Over the age of 18 years
- Age range similar to that of the stroke group

Exclusion Criteria

Potential participants who had any of the following were excluded from the study;

- An inability to engage in the testing due to cognitive, perceptual or communication deficits; as measured by the Mini-mental State Examination (<22/30) and the Star Cancellation Test
- Currently engaged in active physical rehabilitation as defined as regular contact with a rehabilitation health professional
- Another medical condition that could have impacted upon the results, such as another neurological condition, orthopaedic pathology of the lower limbs, or uncontrolled medical problem which would have prevented moderate intensity physical activity
- Contra-indications to TMS including; pacemaker, intracardiac lines, or artificial heart valve containing conductive material; cranio-facial reconstruction or metal implants in head; history of epilepsy or seizures; concussion within the last 6 months; skull fracture or other known skull defects; medication that lowers seizure threshold; history of severe or recurrent headaches
- Where on recruitment, the researchers were unable to elicit a MEP in the target muscle in response to TMS stimulation

7.3.3 Ethical Considerations

Ethical approval was obtained from the Auckland University of Technology Ethics Committee (see Appendix E, Appendix F and Appendix G).

7.3.4 Study Overview

Two identical testing sessions were held seven days apart. During the first testing session, demographic and clinical characteristics of the participants were also gathered, including ethnicity, age, sex, time since stroke onset, type of stroke, medications, and locomotor function as measured by comfortable walking speed (CWS). Measurement of CWS was

conducted on a marked 10m walkway with a stopwatch. With the average to three trials used to determine the average walking speed [327].

TMS testing was carried out on the lesioned hemisphere of participants with stroke. The hemisphere for testing in control participants was randomly selected using a computer generated randomisation plan (www.randomization.com). At each testing session the researchers followed a standardised testing procedure, as outlined in Figure 7-1. Following set up and orientation, baseline force data was gathered during a MVC. Isometric Testing included single and conditioned stimulation to determine cortical excitability, ICI and facilitation ICF. Participants then walked on the treadmill to establish baseline walking parameters. Treadmill Walking Testing included single and conditioned stimulation to determine cortical excitability, ICI and ICF.
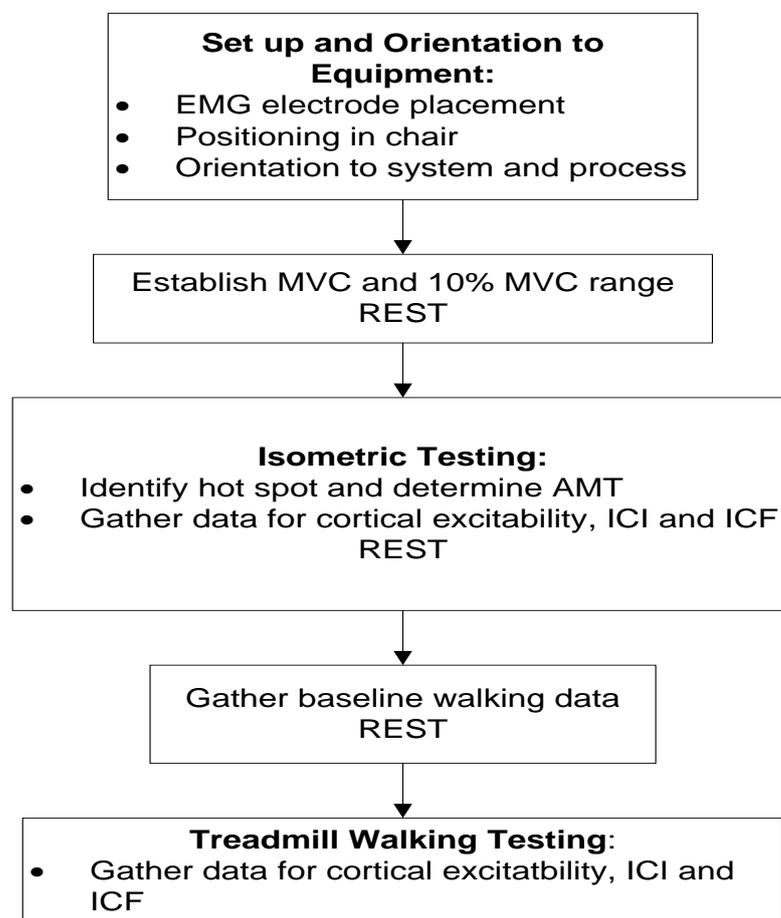
Figure 7-1 TMS Experimental Procedure

7.3.5 Experimental Set-up

Skin preparation for the application of EMG electrodes involved shaving hair from participants with significant body hair, and for all- abrading the skin with fine sandpaper, cleaning the area with alcohol and wiping dry to remove any residue. Skin impedance was evaluated using an Ohmmeter (Dick Smith Electronics, Auckland, NZ) and accepted when less than 5000Ω. Ag/AgCl bipolar electrodes (Norotrode 20, Myotronics Inc., USA) were applied over the soleus muscle as in the position recommended by the SENIAM project group [328]; two thirds of the way between the medial condyle of the femur and the medial malleolus, and aligned in the direction of muscle fibres. EMG recordings were amplified (Octopus AMT-8; Bortec Biomedical, Calgary, Alberta), band-pass filtered (10-1000 Hz), and sampled at 5000 Hz using a data acquisition board (Micro1401, CED, Cambridge). The data were visually displayed and stored for later analysis using Signal software (CED, Cambridge).

For all isometric TMS testing participants were seated in a purpose built chair with the test leg extended (hip 90°, knee 120°, ankle 0°) and fully supported, and the foot strapped to a rigid support which allowed isometric plantar flexion (refer to Figure 7-2). Plantar flexion torque data was collected using a single point load cell (Model PTASP6-E, Precision Transducers Ltd, Auckland, NZ), which had a capacity of up to 300kg and a manufacturer reported combined error of less than 0.02%. Force signals were collected from the load cell at a sampling rate of 2000 Hz. A real time force trace was displayed on an oscilloscope (TDS2014B, Tektronix, Auckland) to provide visual feedback to the participant.
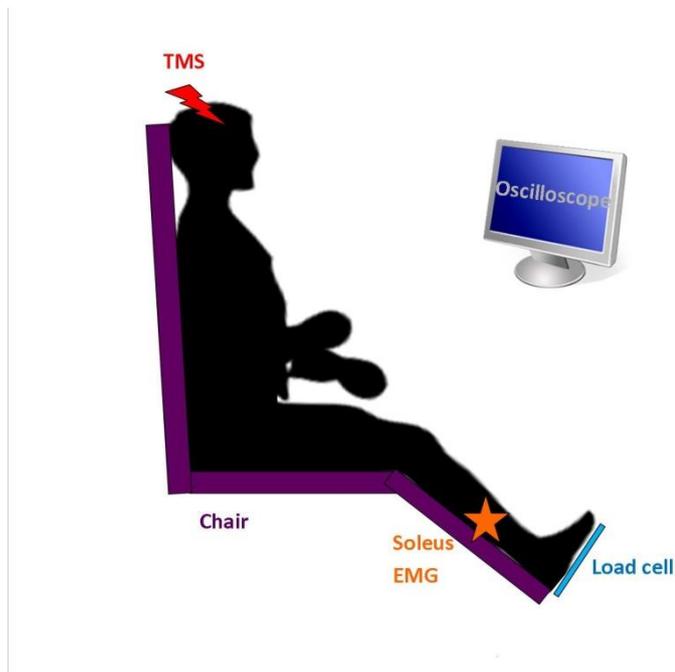
Figure 7-2: Isometric Testing Set-up

During treadmill testing participants were harnessed to a purpose built overhead gantry system using a fall arrest harness (Model 500577, NZ Safety Ltd, Auckland, NZ) and instructed to hold onto a purpose built height adjustable hand rail. The treadmill, a Powerjog GX100 treadmill (Powerjog, United Kingdom) had a slowest speed of 0.03m/s.
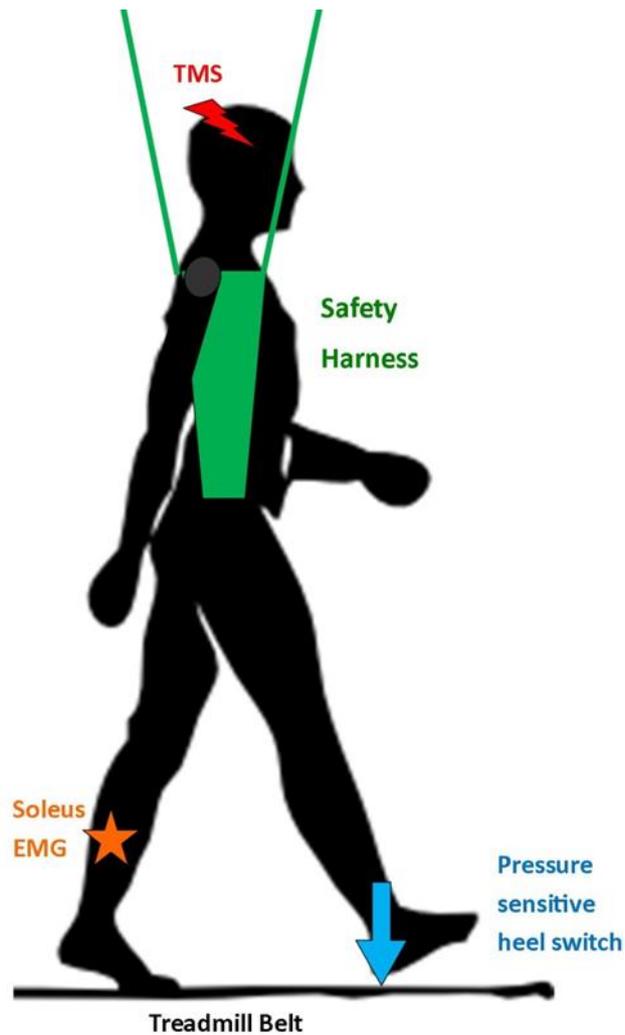
Figure 7-3: Treadmill Walking Set-up

TMS was delivered to the selected hemisphere using a Magstim 200^2 (Magstim, Dyfed, UK) via a double cone coil using monophasic pulses. A tightly fitting neoprene cap marked with a 1cm x 1cm grid relative to the vertex was fitted to the head to ensure maintenance of coil position over the hotspot within and across sessions. The coil was aligned over the hotspot and held in place during isometric testing by a trained research assistant, and secured to the cap using Velcro and an elasticised bandage and then suspended overhead using a system of elasticised straps during treadmill walking.

7.3.6 Isometric Contraction Testing Procedure

MVC was established by completing three, 3-5 second maximal isometric contractions of the plantarflexors with at least three minutes rest between each contraction [329-331]. Participants were provided with continuous, loud verbal encouragement [332] and visual feedback of performance [333].

The juncture of the stimulator coil was placed over the mid-sagittal plane approximately 2cm posterior to the vertex and 1cm contralateral to the tested leg, with a posterior-anterior direction of current flow. The soleus muscle hotspot was identified starting at 30% of the stimulator output and increasing the output in 5% increments until a visually discernable MEP was elicited. Once a discernible MEP was elicited the coil was moved until the coil position which elicited the largest MEP at this stimulus intensity was identified. This location was marked and recorded based on the cap grid system to enable consistent positioning of the coil within and across testing sessions. In participants for whom no MEP could be elicited at rest, a 10%MVC visual target was provided on the oscilloscope and the hotspot procedure was repeated during an active contraction of soleus.

AMT was established by providing a visual target of 10%MVC on the oscilloscope and instructing the participant to match their plantar flexor force to the target force displayed. Using the hotspot position, stimuli were delivered only when the participants' plantar flexor force was 10±2%MVC; the intensity of the stimulator output was reduced by 5% from the value used to determine the hotspot and eight stimuli were applied. If there was a discernible MEP in response to five or more stimuli then the stimulator intensity was reduced by a further 5% until there were less than five visually discernable MEPs in response to eight stimuli. At this point, the stimulus intensity was increased by 1% until five or more out of eight stimuli resulted in a visually discernible MEP. This stimulator intensity was recorded as the AMT.

All single and conditioned TMS were then undertaken at 10%MVC where the stimulator fired only when the participants' plantar flexor force was 10%MVC ±2%MVC. Single pulse TMS was carried out at 120%AMT. Sub threshold conditioning stimuli (70%AMT) were applied at 2.5ms prior to a test stimulus (120%AMT) for ICI, and 15ms prior to the test stimulus for ICF. Ten single pulse stimuli and 10 conditioned stimuli at the two ISIs were delivered in a randomised order, at least five seconds apart.

7.3.7 Treadmill Walking Testing Procedure

Participants were familiarised with the treadmill and secured via the harness and overhead gantry system for safety. The TMS coil was then positioned over the hotspot and secured. The treadmill speed was slowly increased to as close to over ground walking speed as the participant could tolerate. Once a consistent pattern of walking was established and the participant was comfortable, baseline EMG and heel switch data were collected. Timing for the triggering of the TMS stimulation was determined by setting a delay from the heel switch activation on the less affected leg to ensure stimulation of the more affected soleus muscle during its largest burst of activity in the stance phase of gait. TMS stimulation was then repeated in the same format as undertaken during the isometric testing with ten single pulse stimuli and ten conditioned stimuli at the two ISIs, delivered in a randomised order.

7.3.8 Data Processing

Maximal Voluntary Contraction

The highest value of the three trials was recorded and used to calculate the 10%MVC value [96, 99, 101].

Active Motor Threshold

Active motor threshold (AMT) was determined based on the lowest stimulator output which would elicit five or more visually discernible MEP's within eight stimulations.

Background RMS

Background RMS was determined by averaging the ten data signals and measuring using the root mean square amplitude of the EMG activity in a 30ms window prior to stimulation.

MEP Amplitude

The MEP_{AMP} as determined by averaging the ten MEPs and then measuring the maximum peak-to-peak amplitude of the averaged response.

MEP RMS

MEP_{RMS} was determined by rectifying the EMG signals, averaging the ten responses, and then measuring the root mean square amplitude of EMG activity in a 30ms window from MEP onset of the averaged response.

MEP Latency

During isometric testing, MEP latency was determined based on the length of time between stimulation and the onset of a MEP, where onset was calculated as first point at which EMG activity exceeded three standard deviations (SD) of the Background RMS level.

During treadmill testing, MEP latency was visually identified and the length of time between stimulation and the onset of a MEP calculated.

ICI

The extent of ICI was determined by averaging the ten MEPs and measuring the maximum peak-to-peak amplitude of the averaged response; these values were then normalised to the averaged MEP_{AMP} of non-conditioned stimuli.

ICF

The extent of ICF was determined by averaging the ten MEPs and measuring the maximum peak-to-peak amplitude of the averaged response; these values were then normalised to the averaged MEP_{AMP} of non-conditioned stimuli.

7.3.9 Procedure Quality

Table 7-1 provides a summary of the methodological quality of the study procedure using the checklist of recommended factors developed by Chipchase and colleagues [334].

Table 7-1 TMS Procedure Quality

Factor	Reported	Controlled
Participant factors		
Age of participants	Y	Y
Gender of participants	Y	N/A
Handedness of participants	N	N
Subjects prescribed medication	Y	N
Use of CNS active drugs	Y	Y
Presence of neurological/psychiatric disorders in healthy participants	Y	Y
Any medical conditions	Y	Y
History of specific repetitive motor activity	N	N
Methodological factors		
Position and contact of EMC electrodes	Y	Y
Amount of relaxation/contraction of target muscles	Y	Y
Prior motor activity of the muscle to be tested	Y	Y
Level of relaxation of muscles other than those being tested	N	N
Coil type (size and geometry)	Y	Y
Coil orientation	Y	Y
Direction of induced current in the brain	Y	Y
Coil location and stability (with or without a neuronavigation system)	Y	Y
Type of stimulator used (e.g. brand)	Y	Y
Stimulation intensity	Y	Y
Pulse shape (monophasic or biphasic)	Y	Y
Determination of optimal hotspot	Y	Y
The time between MEP trials	Y	Y
Time between days of testing	Y	Y
Subject attention (level of arousal) during testing	Y	Y
Method for determining threshold (active/resting)	Y	Y
Number of MEP measures made	Y	Y
Paired pulse only		
Intensity of test pulse	Y	Y
Intensity of conditioning pulse	Y	Y
Inter-stimulus interval	Y	Y
Analytical factors		
Method for determining MEP size during analysis	Y	Y
Size of unconditioned MEP	Y	Y

7.3.10   Data Analysis

Data analysis was performed using SPSS software package (version 19) [286]. Inspection of raw data and testing for the normality of the distribution of the dependent variables using the Shapiro-Wilks Test was undertaken to evaluate the distribution of all continuous variables, where variables were identified as non-normally distributed the distribution was graphically reviewed. Data analysis involved descriptive analysis of group characteristics and test-retest reliability of corticomotor excitability measures. For all statistical analyses a significance level of p<.05 was set.

Descriptive analysis of group characteristics provided information on the participants age, sex, hemiplegia and time since stroke (where relevant). Descriptive analysis including mean, standard deviation and range provided information of corticomotor excitability measures taken during the first testing session for isometric testing (MVC, AMT, Background RMS, MEP$_{AMP}$ MEP$_{RMS}$, Latency, ICI$_{AMP}$, ICI$_{RMS}$, ICF$_{AMP}$, ICF$_{RMS}$) and measures taken during Treadmill testing (Treadmill walking speed, Background RMS, MEP$_{AMP}$ MEP$_{RMS}$, Latency, ICI$_{AMP}$, ICI$_{RMS}$, ICF$_{AMP}$, ICF$_{RMS}$) was undertaken.

Intra and inter-session test-retest reliability of measures of were evaluated using two-tailed paired t-tests, intra-class correlation coefficients (ICC), typical error (TE) and the standard error of the measure (SEM). The two-tailed paired t-tests determines whether the group mean changed over time (where p>0.05). A two-way random, absolute agreement ICC provides an assessment of the reproducibility of the rank order of the participants on a given measure, while the 95% confidence interval indicates the likely range of the ICC in the true population [287]. ICC values were interpreted based on Landis and Koch standards for strength of agreement; 0 – 0.2 (poor), 0.2 – 0.4 (fair), 0.4 – 0.6 (moderate), 0.6 – 0.8 (good) and 0.8 – 1.0 (excellent) [288]. TE is a measure of within-subject variability encapsulating both biological variability and technical error inherent in the measure. It provides an indication of the precision of the measure which is not influenced by the heterogeneity of the sample[289]. TE was calculated using the equation

$$TE = \left(\frac{Sdiff}{\sqrt{2}} \right)$$

where S$_{diff}$ is the standard deviation of the individual difference scores between measurement 1 and measurement 2 [281]. To enable comparison of within-subject variability across measures, the coefficient of variation of TE was also calculated. SEM is the standard error in an observed score and is calculated using the equation

$$SD * \sqrt{1 - r_{xx}}$$

where *SD* is the standard deviation of measurement 1 and r_{xx} is the coefficient of reliability of measurement 1 and measurement 2, in this case ICC. SEM is usually presented as a raw value, however it can be referenced to the mean of measurement 1 (also known as the CV of SEM) to enable comparison between measures, studies and groups with differing ranges of scores, such as between healthy participants and those with stroke. Intra-session reliability of background RMS, MEP_{AMP} MEP_{RMS}, and Latency were established and inter-session reliability of MVC, AMT, Background RMS, MEP_{AMP} MEP_{RMS}, Latency, ICI_{AMP}, ICI_{RMS}, ICF_{AMP}, ICF_{RMS} during isometric testing and treadmill walking were established.

7.3.11   Data Accuracy Screening

Following data collection and processing, data was screened. Visual checking of raw data revealed errors in the saving and storage of the data for one stroke participant. This data was consequently excluded from the analysis. An operator error meant that the second testing session for Case 6 did not include conditioned stimuli during the gait testing; this data is therefore absent from the analysis.

Cross checking of data entered into SPSS (version 19) against raw data was carried out to ensure the accuracy of data entry. Data from 20% of the total sample (two stroke participants and three control participants) were randomly selected for cross checking. No inconsistencies were identified. Visual checking of the range of scores and consideration of the plausibility of the mean and standard deviation for each variable also revealed no inconsistencies. Outlier values were identified on a number of measures. When statistical testing was repeated with exclusion of the outlier values, no difference in the outcome of any of the statistical tests was noted. Therefore, outlier values were included in all statistical analyses.

7.4 Results

7.4.1 Recruitment and Retention

Twenty healthy participants volunteered for the study, of which four were excluded due to a contraindication to TMS. Two healthy participants withdrew from the study *during* the first testing session, both due to an inability to tolerate the TMS stimulus, consequently a total of 14 control participants were analysed. Of the 21 people with stroke who volunteered for the study, two were excluded due to a contraindication to TMS. Six stroke

participants withdrew from the study *during* the first testing session; two were unable to tolerate the TMS stimulus and in four participants a MEP in soleus could not be elicited. The data for one participant with stroke was removed from the analysis due to technical errors in data saving and storage, resulting in 12 participants with stroke included in the final analysis (refer to Figure 7-4). Data collection was completed from July 2009 to April 2010.

Control Participants

Volunteered
(n=20)

Did not meet eligibility criteria (n=4)

- Past medical history contraindicates TMS (n=2)
- Current medication contraindicates TMS (n=2)

Eligible
(n=16)

Consented
(n=16)

Withdrew from study prior to first testing session (n=2)

- Unable to tolerate stimulation (n=2)

Completed
(n=14)

Analysed
(n=14)

Stroke Participants

Volunteered
(n=21)

Did not meet eligibility criteria (n=2)

- Current medications contraindicates TMS (n=2)

Eligible
(n=19)

Consented
(n=19)

Withdrew from study prior to first testing session (n=6)

- Unable to tolerate stimulus (n=2)
- No MEP could be elicited on testing (n=4)

Completed
(n=13)

Data removed from analysis (n=1)

- Technical errors in data saving (n=1)

Analysed
(n=12)

Figure 7-4: Recruitment and Retention of Stroke and Healthy Participants

7.4.2 Descriptive Analysis

Sample Characteristics

The mean age of the stroke sample was 56.8 years (SD=20.3, range 22-78), with seven male (58%) and five female (42%) participants. The mean age of the control sample was 54.6 years (SD=13.5, range 26-73), with five male (36%) and nine female (64%) participants. The mean CWS of the control group was 1.43m/s (SD=0.22, range 1.13-1.67m/s). The mean CWS of the stroke group was 0.89m/s (SD=0.37, range 0.44-1.33m/s). Five participants in the stroke group had right hemiplegia (42%) and seven participants had left hemiplegia (58%). The mean time since onset of stroke was 52.8 months (range 7-136).

Isometric Testing

The results of the TMS derived measures of corticomotor excitability during an isometric contraction in both the control and the stroke groups are shown in Table 7-2.

Table 7-2 TMS Measures during an Isometric Contraction

	Control Group (n=14)			Stroke Group (n=12)		
	Mean	SD	Range	Mean	SD	Range
MVC (Nm)	274	147	98 - 490	186	88	78 - 392
AMT (%SO)	55	6	44 - 65	58	7	45 - 72
Background RMS (mV)	0.013	0.008	0.005 - 0.031	0.010	0.006	0.002 - 0.022
MEP_{AMP} (mV)	0.097	0.089	0.015 - 0.334	0.037	0.019	0.012 - 0.070
MEP_{RMS} (mV)	0.029	0.021	0.007 - 0.081	0.017	0.011	0.000 - 0.035
Latency (s)	0.038	0.003	0.032 - 0.043	0.041	0.005	0.031 - 0.052

Note: MVC=Maximal voluntary contraction, AMT=Active motor threshold, RMS=Root mean square, MEP_{AMP} = MEP Amplitude, MEP_{RMS} = MEP Root mean square

The range, mean and standard deviation of the conditioned TMS measures during an isometric contraction for both the control and stroke groups are shown in Table 7-3 as normalised values.

Table 7-3 Conditioned TMS measures during an Isometric Contraction

	Control Group (n=14)			Stroke Group (n=12)		
	Mean	SD	Range	Mean	SD	Range
ICI_{AMP} (%)	71	29	27 - 127	90	33	24 - 144
ICI_{RMS} (%)	85	24	49 - 140	82	27	31 - 121
ICF_{AMP} (%)	166	98	57 - 452	153	82	68 - 325
ICF_{RMS} (%)	168	58	82 - 293	197	123	93 - 484

Note: ICI_{AMP}=Intracortical inhibition amplitude, ICI_{RMS}=Intracortical inhibition root mean square, ICF_{AMP} =Intracortical facilitation amplitude, ICF_{RMS} =Intracortical facilitation root mean square

Treadmill Walking

The range, mean and standard deviation of the conditioned TMS measures during treadmill walking parameters are displayed in Table 7-4.

Table 7-4 TMS Measures during Treadmill Walking

	Control Group (n=14)			Stroke Group (n=12)		
	Mean	SD	Range	Mean	SD	Range
Walking Speed (m/s)	1.14	0.18	0.75 - 1.39	0.72	0.32	0.28 - 1.14
Background RMS (mV)	0.069	0.044	0.110 - 0.151	0.046	0.027	0.014 - 0.105
MEP_{AMP} (mV)	0.765	0.505	0.151 - 2.110	0.546	0.843	0.047 - 3.027
MEP_{RMS} (mV)	0.215	0.141	0.049 - 0.573	0.151	0.209	0.023 - 0.767
Latency (s)	0.035	0.004	0.028 - 0.041	0.040	0.009	0.030 - 0.059

Note: RMS=Root mean square, MEP_{AMP} = MEP Amplitude, MEP_{RMS} = MEP Root mean square

The results of the conditioned measures taken during treadmill walking for both the control and the stroke groups are shown in Table 7-5.

Table 7-5 Conditioned TMS Measures during Treadmill Walking

	Control Group (n=14)			Stroke Group (n=12)		
	Mean	SD	Range	Mean	SD	Range
ICI_{AMP} (%)	99	33	55 - 192	89	35	42 - 162
ICI_{RMS} (%)	94	17	62 - 121	96	36	59 - 198
ICF_{AMP} (%)	94	26	61 - 141	92	23	634 - 138
ICF_{RMS} (%)	91	23	45 - 128	95	19	61 - 123

Note: ICI_{AMP}=Intracortical inhibition amplitude, ICI_{RMS}=Intracortical inhibition root mean square, ICF_{AMP} =Intracortical facilitation amplitude, ICF_{RMS} =Intracortical facilitation root mean square

7.4.3 Reliability Analysis

The aim of this study was to evaluate the reliability of TMS measures of corticomotor excitability of the soleus muscle during an isometric contraction and during treadmill walking in healthy people and people with stroke. This section describes intra- and inter-session reliability for measures taken during an isometric muscle contraction and the inter-session reliability for measures taken during treadmill walking.

Intra-session Reliability during an Isometric Contraction

The intra-session ICC, ICC 95% confidence interval, TE and SEM of the Background RMS, MEP_{AMP}, MEP_{RMS} and latency are presented in Table 7-6.

Table 7-6 Intra-session Reliability of TMS during an Isometric Contraction

		Control (n=14)	Stroke (n=12)
Background RMS	ICC (95% CI)	0.74 (0.19-0.92)	0.84 (0.47-0.95)
	TE (CV)	0.008 (65%)	0.004 (40%)
	SEM (CV)	0.004 (31%)	0.003 (30%)
MEP_{AMP}	ICC (95% CI)	0.87 (0.58-0.96)	0.84 (0.47-0.93)
	TE (CV)	0.045 (47%)	0.015 (41%)
	SEM (CV)	0.032 (33%)	0.008 (22%)
MEP_{RMS}	ICC (95% CI)	0.85 (0.69-0.97)	0.81 (0.37-0.94)
	TE (CV)	0.013 (44%)	0.007 (38%)
	SEM (CV)	0.008 (28%)	0.005 (29%)
Latency	ICC (95% CI)	0.60 (-0.33-0.87)	0.67 (-0.16-0.91)
	TE (CV)	0.002 (6%)	0.003 (8%)
	SEM (CV)	0.002 (5%)	0.003 (7%)

Note: RMS=Root mean square, MEP_{AMP} = MEP Amplitude, MEP_{RMS} = MEP Root mean square, ICC=Intra-class correlation coefficient, TE=Typical Error, SEM=Standard error of the measure, CV=Coefficient of variation

Paired t-tests between measurement 1 and 2 were not significant for any of the outcome measures in either of the groups (all p>0.05), indicating no absolute systematic bias. Background RMS demonstrated good intra-session reliability in the control group and

excellent intra-session reliability in the stroke group. The within-subject variability was substantial, with both absolute and relative TE larger in the control group than the stroke group. The CV of SEM for Background RMS was comparable between groups.

MEP_{AMP} demonstrated excellent intra-session reliability in the control group and the stroke group. The absolute within-subject variability was much larger in the control group than the stroke group. However, the CV of TE was similar between the groups, indicating modest within-subject variability in both groups. The standard error for MEP_{AMP} was larger in the control group than the stroke group.

MEP_{RMS} values demonstrated excellent intra-session reliability and modest within-subject variability and CV of SEM in both groups. Latency measures demonstrated good intra-session reliability in the control group and the stroke group. Both groups had similarly low levels of absolute and relative within-subject variability and comparable SEM's.

In summary, it was hypothesised that both stroke and control groups would demonstrate good to excellent intra-session reliability (≥0.6) on measures of corticomotor excitability of the soleus muscle during an isometric contraction. This hypothesis was supported for all measures, with most measures demonstrating excellent intra-session reliability in both groups.

Inter-session Reliability during an Isometric Contraction

Paired t-tests between measurement 1 and 2 were not significant for any of the outcome measures in either of the groups (all $p > 0.05$), indicating no absolute systematic bias.

The inter-session reliability including ICC, ICC 95% confidence interval, TE and SEM of the MVC, AMT, Background RMS, MEP_{AMP} and MEP_{RMS} and latency during an isometric contraction are presented in Table 7-7.

Table 7-7 Inter-session Reliability during an Isometric Contraction

		Control (n=14)	Stroke (n=12)
MVC (Nm)	ICC (95% CI)	0.83 (0.49-0.95)	0.74 (0.13-0.92)
	TE (CV)	8 (27%)	7 (37%)
	SEM (CV)	6 (21%)	5 (24%)
AMT (%SO)	ICC (95% CI)	0.85 (0.76-0.97)	0.69 (0.21-0.90)
	TE (CV)	4 (5%)	5 (8%)
	SEM (CV)	3 (5%)	4 (6%)
Background RMS	ICC (95% CI)	0.95 (0.83-0.98)	-1.15 (-11.48-0.45)
	TE (CV)	0.003 (22%)	0.006 (61%)
	SEM (CV)	0.002 (16%)	UTC
MEP$_{AMP}$	ICC (95% CI)	0.83 (0.26-0.80)	0.29 (-1.20-0.84)
	TE (CV)	0.043 (44%)	0.056 (150%)
	SEM (CV)	0.037 (38%)	0.016 (43%)
MEP$_{RMS}$	ICC (95% CI)	0.90 (0.69-0.97)	0.22 (-2.15-0.76)
	TE (CV)	0.008 (29%)	0.014 (79%)
	SEM (CV)	0.007 (24%)	0.010 (58%)
Latency (s)	ICC (95% CI)	0.73 (0.14-0.91)	0.64 (-0.15-0.89)
	TE (CV)	0.002 (5%)	0.004 (9%)
	SEM (CV)	0.002 (5%)	0.003 (7%)

Note: MVC=Maximal voluntary contraction, AMT=Active motor threshold, RMS=Root mean square, MEP$_{AMP}$ = MEP Amplitude, MEP$_{RMS}$ = MEP Root mean square, ICC=Intra-class correlation coefficient, TE=Typical Error, SEM=Standard error of the measure, CV=Coefficient of variation, UTC= Unable to calculate

The reliability of MVC was excellent for the control group and good for the stroke group. The absolute within-subject variability was larger in the control group than the stroke group, with greater relative within subject variability in the stroke group than the control group. SEM was modest, and comparable between the groups.

AMT demonstrated excellent reliability in the control group and good reliability in the stroke group. The absolute and relative within-subject variability and standard error were low, although they were slightly larger in the stroke group than the control group.

Background RMS values demonstrated excellent test-retest reliability in the control group and poor reliability in the stroke group. Absolute and relative within-subject variability was larger in the stroke group than the control group. The SEM could not be calculated in the stroke group due to the poor reliability.

MEP$_{AMP}$ demonstrated excellent reliability in the control group and poor reliability in the stroke group. The relative within-subject variability was modest in the control group and very large in the stroke group. The absolute standard error was greater in the control group than the stroke group; however the relative standard error was larger in the stroke group.

MEP$_{RMS}$ values demonstrated excellent reliability in the control group and poor reliability in the stroke group. Absolute and relative within-subject variability and standard error were larger in the stroke group than the control group. Latency measures demonstrated good test-retest reliability both groups. Both groups had low levels of within-subject variability and standard error, although the stroke group values were slightly larger than the control groups.

Hypotheses 2 and 3 stated that; the control group would demonstrate good to excellent inter-session reliability (≥ 0.6), and that the stroke group would demonstrate poor to adequate inter-session reliability (≤ 0.59) on measures of corticomotor excitability of the soleus muscle during an isometric contraction. These hypotheses were supported for non-conditioned measures, except for latency which demonstrated good reliability in the stroke group.

Table 7-8 presents the inter-session reliability of the conditioned measures (normalised values) taken during an isometric contraction.

Table 7-8 Inter-session Reliability of Conditioned Measures during an Isometric Contraction

		Control (n=14)	Stroke (n=12)
ICI_{AMP} (%)	ICC (95% CI)	-0.53 (-5.34-0.55)	0.16 (-0.98-0.72)
	TE (CV)	41 (59%)	27 (30%)
	SEM (CV)	36 (51%)	30 (33%)
ICI_{RMS} (%)	ICC (95% CI)	-0.32 (-2.82-0.56)	0.26 (-0.71-0.75)
	TE (CV)	27 (32%)	25 (30%)
	SEM (CV)	27 (32%)	23 (28%)
ICF_{AMP} (%)	ICC (95% CI)	0.00 (-2.21-0.68)	-0.56 (-6.27-0.57)
	TE (CV)	77 (47%)	56 (36%)
	SEM (CV)	98 (59%)	103 (67%)
ICF_{RMS} (%)	ICC (95% CI)	0.44 (-0.87 -0.82)	0.10 (-1.75-0.73)
	TE (CV)	52 (29%)	95 (64%)
	SEM (CV)	43 (26%)	117 (59%)

Note: ICI_{AMP}=Intracortical inhibition amplitude, ICI_{RMS}=Intracortical inhibition root mean square, ICF_{AMP} =Intracortical facilitation amplitude, ICF_{RMS} =Intracortical facilitation root mean square, ICC=Intra-class correlation coefficient, TE=Typical Error, SEM=Standard error of the measure, CV=Coefficient of variation

All conditioned measures demonstrated poor test-re-test reliability in both groups, except the ICF RMS which had moderate reliability in the control group and ICI_{RMS} which had fair reliability in the stroke group. Within-subject variability and standard error were comparable between the groups, except in ICI_{AMP} which were larger in the control group and ICF_{RMS} which were larger in the stroke group.

Hypotheses 2 and 3 stated that; the control group would demonstrate good to excellent inter-session reliability (≥0.6), and that the stroke group would demonstrate poor to adequate inter-session reliability (≤0.59) on measures of corticomotor excitability of the soleus muscle during an isometric contraction. These hypotheses were supported for the stroke group with all conditioned measures demonstrating poor to fair reliability. In contrast to what was hypothesised, conditioned measures in the control group also demonstrated poor to moderate reliability.

Inter-session Reliability during Treadmill Walking

Table 7-9 presents the inter-session reliability of TMS measures taken during treadmill walking in both groups.

Table 7-9 Inter-session Reliability during Treadmill Walking

		Control (n=14)	Stroke (n=12)
Background RMS	ICC (95% CI)	0.54 (-0.48-0.85)	0.76 (0.13-0.93)
	TE (CV)	0.032 (47%)	0.021 (45%)
	SEM (CV)	0.030 (43%)	0.013 (28%)
MEP_{AMP}	ICC (95% CI)	0.31 (-1.26-0.78)	0.94 (0.78-0.98)
	TE (CV)	0.373 (49%)	0.276 (51%)
	SEM (CV)	0.420 (55%)	0.207 (38%)
MEP_{RMS}	ICC (95% CI)	0.41 (-0.44-0.79)	0.91 (0.68-0.98)
	TE (CV)	161.27 (41%)	114.819 (40%)
	SEM (CV)	0.108 (50%)	0.063 (42%)
Latency	ICC (95% CI)	0.79 (0.37-0.93)	0.89 (0.62-0.97)
	TE (CV)	0.002 (6%)	0.004 (9%)
	SEM (CV)	0.002 (6%)	0.003 (8%)

Note: RMS=Root mean square, MEP_{AMP} = MEP Amplitude, MEP_{RMS} = MEP Root mean square, ICC=Intra-class correlation coefficient, TE=Typical Error, SEM=Standard error of the measure, CV=Coefficient of variation

Background RMS values demonstrated moderate test-retest reliability in the control group and good reliability in the stroke group. Relative within-subject variability was modest and comparable in both groups. Absolute and relative SEM was smaller in the stroke group than the control group.

MEP_{AMP} demonstrated fair reliability in the control group and excellent reliability in the stroke group. Absolute and relative within-subject variability was modest and comparable between the groups. Absolute and relative standard error was smaller in the stroke group than the control group.

MEP_{RMS} values demonstrated moderate reliability in the control group and excellent reliability in the stroke group. Within-subject variability was modest and comparable in both groups; whilst standard error was larger in the control group.

Latency measures demonstrated good reliability in the control group and excellent reliability in the stroke group. Both groups had very low levels of within-subject variability and standard errors; however values were slightly higher in the stroke group.

Hypothesis four stated that the control and stroke groups would demonstrate good to excellent inter-session reliability (ICC≥0.6) on measures of corticomotor excitability of the soleus muscle during a walking task. This hypothesis was supported for non-conditioned

measures in the stroke group, with all measures demonstrating excellent reliability. However this hypothesis was not supported for the control group; where non-conditioned measures demonstrated fair reliability, except latency which had good reliability.

The inter-session reliability of conditioned measures taken during treadmill walking for both groups are presented in Table 7-10.

Table 7-10 Inter-session Reliability of Conditioned Measures during Treadmill Walking

		Control (n=13)	Stroke (n=12)
ICI_{AMP} (%)	ICC (95% CI)	0.26 (-1.49-0.78)	-0.91 (-5.09-0.44)
	TE (CV)	33 (33%)	49 (55%)
	SEM (CV)	28 (28%)	UTC
ICI_{RMS} (%)	ICC (95% CI)	0.08 (-1.07-0.68)	0.51 (-0.73-0.86)
	TE (CV)	19 (19%)	23 (24%)
	SEM (CV)	16 (17%)	25 (26%)
ICF_{AMP} (%)	ICC (95% CI)	0.32 (-1.51 -0.80)	-0.06 (-0.74-0.64)
	TE (CV)	25 (25%)	34 (36%)
	SEM (CV)	21 (22%)	UTC
ICF_{RMS} (%)	ICC (95% CI)	0.66 (-0.17 -0.90)	-0.44 (-0.30-0.82)
	TE (CV)	17 (18%)	16 (17%)
	SEM (CV)	13 (15%)	UTC

Note: ICI_{AMP}=Intracortical inhibition amplitude, ICI_{RMS}=Intracortical inhibition root mean square, ICF_{AMP} =Intracortical facilitation amplitude, ICF_{RMS} =Intracortical facilitation root mean square, UTC= Unable to compare, ICC=Intra-class correlation coefficient, TE=Typical Error, SEM=Standard error of the measure, CV=Coefficient of variation

Conditioned measures varied in reliability estimates with the control group demonstrating poor reliability in ICI_{RMS}, fair reliability for ICI_{AMP} and ICF_{AMP} and good reliability in ICF_{RMS}. Whilst in the stroke group all measures demonstrated poor reliability except ICI_{RMS} which had moderate reliability. Within-subject variability was comparable between the groups. In contrast to the stated hypothesis conditioned measures of corticomotor excitability frequently displayed poor to fair reliability in both groups when evaluated during a locomotor task.

7.5 Discussion

This section discusses the results of the current study in light of those previously reported in healthy and stroke populations; and considers the potential explanations for the study findings based on the study method, the sample characteristics, and the physiological changes which occur following stroke .

7.5.1 Study Samples

Study participants volunteered to take part, which is likely to have introduced a significant selection bias in both the control and stroke groups; in all likelihood the samples represent people who are relatively healthy and physically active. Matching with control participants appeared to be largely successful with the groups being similar in terms of age. However, there was a difference in the gender balance between the groups; with a larger proportion of females in the control group. This may be relevant, as pre-menopausal female participants tend to have greater variability in TMS-derived measures of corticomotor excitability due to hormonal fluctuations [335, 336]. As expected, there were marked differences between the stroke group and the control group in terms of physical function; the stroke participants had on average a slower treadmill walking speed than the control participants.

The stroke sample reflected a group of people with mild to severe chronic stroke. In comparison to previous studies investigating the reliability of TMS-derived measures of lower limb corticomotor excitability in people with stroke [245, 337] the sample in the current study represents a group with a wide age range (22-78 years), who are on average longer since stroke, with a wide range of physical disability. Unlike previous studies which tend to include people with stroke who have very mild physical disability, the intention was to recruit participants who would likely be suitable for a clinical trial investigating locomotor rehabilitation following stroke. This may have resulted in a heterogeneous sample which is more representative of the source population than previous research.

Other factors not controlled for in this experimental process may have influenced the internal validity of the study. Caffeine consumption, medications, levels of physical activity and footedness may be potential confounders [334].

In summary; the characteristics of age, time since stroke and level of physical disability of the participants in this study is dissimilar to the participants of previous studies investigating TMS-derived measures of corticomotor excitability in people following

stroke. These differences are important in that they provide an indication of the reliability of these measures in a sample more representative of the stroke population than those previously reported. However, a number of factors have been highlighted related to recruitment, inclusion and exclusion criteria and sample characteristics which challenge the internal and external validity of the current study.

7.5.2 Corticomotor and Intra-cortical Excitability in People with Stroke

Descriptive analysis indicates that on average, the stroke group had a higher active motor threshold, a longer latency, and a smaller MEP_{AMP} and MEP_{RMS} than age matched healthy participants both during a 10%MVC isometric contraction and during a walking task. These findings highlight that people with stroke have reduced corticomotor excitability; longer conduction times for transmission of an action potential from the primary motor cortex to the soleus muscle and likely activate a smaller number of cortico-spinal motor neurons when stimulated with TMS over the primary motor cortex. These findings concur with previous studies investigating TMS-derived measures of corticomotor excitability in people with stroke during an isometric contraction and at rest [176, 245, 250, 253, 337].

The results of the conditioned measures show that normalized values for ICI and ICF amplitude and RMS were similar between the groups in both isometric testing and treadmill testing. This is contrast to previous studies which show less inhibition in stroke participants when compared to healthy people [338-341]. This may relate to the fact that ICI was measured during a low level isometric contraction in the current study, whereas previous studies have measured ICI at rest. It may also relate to differences in the muscle tested, the severity in deficit following stroke, or the time since stroke.

7.5.3 Intra-Session Reliability of TMS-derived Measures during an Isometric Contraction

The first hypothesis of this study was that the control and stroke groups would demonstrate good to excellent intra-session reliability (ICC ≥0.6) for measures of corticomotor excitability of the soleus muscle during an isometric contraction. This hypothesis was supported for all measures, in both groups.

Motor Evoked Potential Amplitude

MEP_{AMP} intra-session reliability was excellent in both stroke and control groups. These findings can be compared to three previous studies investigating intra-session reliability in healthy people in the upper limb [342-344], however, no studies were identified which investigated intra-session reliability in the lower limb. Bastani and colleagues [342] and Christie and colleagues [343] investigated the extensor carpi radialis and the first dorsal interossei (FDI) and Adductor Digiti Minimi respectively, both reporting excellent intra-session reliability. In contrast, McDonnell and colleagues reported poor to moderate intra-session reliability of MEP_{AMP} in Flexor Carpi Ulnaris and FDI [344]. They found ICCs of between 0.16 and 0.55 following stimulation at 110% and 120% of RMT. However, the results of McDonnell and colleagues work may be explained by the small number of stimuli applied at each intensity (five) and that stimulation was applied at rest [344], although Bastani and colleagues used a similar protocol and reported much higher ICC's [342]. No studies were identified which investigated intra-session reliability of MEP_{AMP} in people with stroke. Intra-session reliability in the stroke group was similar to that found in the control group, indicating that MEP_{AMP} is a reliable intra-session measure of corticomotor excitability in the lower limb of people with stroke.

Within subject variability can be represented by TE to provide an indication the biological variability and technical error within a measure; it is suggested that the CV of TE should fall under 10% for a measure to be considered precise and accurate [281]. No previous intra-session reliability studies using TMS have reported TE, although a number of previous researchers have described the variability in MEP_{AMP} by calculating CV within a block of TMS stimuli for an individual [251, 345]. However, this does not reflect the influence of averaging the raw values in a block of stimuli to generate a MEP_{AMP} value, nor the effect of test-retest on variance. In the current study, intra-session CV of TE values were comparable between the groups at 47% in the control group and 41% in the stroke group This represents substantial within-subject variability in $MEP_{AMP.}$ Based on Hopkins work it is suggested that an individual would need to change by 1.5 to two times the CV of TE to be considered a true change [281]. In this sample, a control participant would need to change their MEP_{AMP} value by +/-71% and a stroke participant by +/-62% within a session to be considered a true change

Methodological factors may introduce variability to the MEP_{AMP} measure, including the level of muscle pre-activation [251, 346, 347]; the stimulus intensity [251, 346]; the coil shape, orientation, position, and extraneous movement of the coil [346, 348]; electrode

position [349]; the age of the participants [335, 350]; the muscle under investigation [347, 351]; the length of time between testing blocks, whether the testing protocol includes a familiarisation period [347, 352]; and the number of MEPs included in MEP_{AMP} average [342, 343, 347]. In this study, considerable effort was made to reduce potential sources of variability. However, variability may have been introduced by studying a distal lower limb muscle, the use of a double cone coil shape where, due to the focal nature of the stimulation field, a small change in position or orientation may have a significant impact on MEP_{AMP} [346, 353, 354], use of conventional methods to standardise coil position rather than neuronavigation [355], the lack of a familiarisation session [347, 352], and the relatively novice experience level of the TMS operators [349].

However, much of the within-subject variability observed in MEP_{AMP} may be explained by biological variability. MEP_{AMP} reflects the efficacy and excitability of the corticomotor tract and it is acknowledged that there is significant biological variability inherent in the corticomotor system [353]. Biological variability may be present at many levels of the system including; the degree of attention the participant is giving the task at any given time [346], fluctuations in inter-hemispheric and intra-cortical excitability, fluctuations in the contribution of sub-cortical and spinal inputs to the corticomotor pathway and fluctuations in motor neuron excitability [356-358]. Generation of plantar flexion force potentially involves contributions from many synergists (gastrocnemius, soleus, tibialis posterior, flexor halucis longus, flexor digitorum longus and plantaris). The muscle under investigation in the current study was the Soleus; inconsistency in the contribution of synergists to the plantar flexion action may have introduced variability to the level of activity in the soleus muscle during TMS testing. However, the excellent intra-session reliability of the soleus muscle Background RMS suggests that this was not a significant contributor. Rosler and colleagues[359] indicated that, in healthy participants, approximately two thirds of the trial-to-trial variability in MEP_{AMP} could be ascribed to variability in the number of activated motor units, presumably due to fluctuations in corticomotor excitability. The balance of the variability was explained by desynchronisation of descending action potentials [359]. Desynchronisation of descending action potentials, which results in phase cancellation, can reduce MEP_{AMP} by up to 32-88% when compared to responses to maximal peripheral stimulation in healthy adults [356-358]. There is considerable inter-individual variation in the degree of desynchronisation in healthy participants and it may be anticipated that desynchronisation would result in greater within-subject variability in $MEP_{AMP,}$ with less influence on MEP_{RMS} [357]. However, the CV of TE in MEP_{AMP} and MEP_{RMS} in both groups were similar, suggesting that other sources of variability play a greater role in biological variability than

desynchronisation. At times after a TMS stimulus, alpha motor neurons have been shown to discharge multiple times. This is identified as another potential source of biological variability in MEP$_{AMP}$ and is ascribed to changes in cortical and spinal, but not sub-cortical, excitability [358]. Repetitive discharges are more likely to occur at higher stimulation intensities and muscle pre-activation levels; therefore, they may be less of a contributor to within-subject variability in MEP$_{AMP}$ in the current study. However, they are also more likely in response to fatiguing contractions [360]. Whilst there was no evidence of fatigue in either control or stroke participants in the current study, this effect cannot be ruled out. A recent study also showed that repetitive motor neuron discharges increase in response to dexterity but not strength training [361]. The current study required participants to sustain a 10%MVC contraction, which is a relatively dexterous task, potentially influencing the amount of repetitive motor neuron discharges and introducing greater biological variability.

Given the deficits in corticomotor excitability seen in people with stroke it might be expected that the within-subject variability introduced by fluctuations in corticomotor excitability would be greater in the stroke group than the control group [253]. However, the absolute intra-session within-subject variability was less in the stroke group than the control group, and the relative within-subject variability was similar. Regardless, it is important to note that there is substantial within-subject variability in MEP$_{AMP}$ on test – retest within a single session in both control and stroke participants and this value provides important information for the interpretation of what represents meaningful change in MEP$_{AMP}$ within a single testing session [281].

SEM is an alternative measure of reliability which indicates the standard error in an observed score. SEM considers the sample heterogeneity, the rank order of participants and within-subject variability. In the current study, the SEM for MEP$_{AMP}$ was 0.032mV in the control group and 0.008mV in the stroke group. These values represent 33% and 22% of the respective group means of measurement 1, indicating that the relative standard error is greater in the control group than the stroke group for MEP$_{AMP}$. SEM has been presented in one other study which investigated the intra-session reliability of TMS-derived measures of corticomotor excitability in healthy participants [342]. However the SEM's provided were not consistent with SEM's calculated from the SD and ICC's published using the equation;

$$SEM \ = SD * \sqrt{1 - Rxx} \ .$$

CV of SEM's calculated from the published data have a range of 5-22%. The slightly larger SEM for MEP$_{AMP}$ in the control group in the current study when compared to the work of Bastani and colleagues may relate to methodological differences such as the parameters of stimulation, differences in the sample dispersion or may reflect that MEP's from upper limb muscles are less variable than those from lower limb muscles.

Motor Evoked Potential Root Mean Square

No studies were identified which reported intra-session ICC's for MEP$_{RMS}$ in either healthy participants or controls. Previous research has demonstrated the strong correlation between MEP$_{RMS}$ and MEP$_{AMP}$ measures [347]. The current study concurs with this work, as the MEP$_{RMS}$ ICC's , CV of TE and CV of SEM values were all similar to those in the MEP$_{AMP}$ measure in both groups; indicating similar levels of reliability, within-subject variability and standard error in both measures.

Latency

As hypothesised the present study reported good intra-session reliability for latency in both groups. Previous research reports intra-session ICC's for MEP latency of between 0.75 [342] and 0.93 [362] in healthy populations. No studies were identified which investigated intra-session reliability of latency in people with stroke. The present study reports an ICC which is less than previously reported results. However, the within-subject variability is small (CV of TE Control=6%, Stroke=8%) suggesting that the measure is precise. The CV of SEM was 5% in the control group and 7% in the stroke group, which is slightly higher than the 2-3% previously reported by other authors in healthy populations [342, 362]. Nonetheless, it should be noted that the sample dispersion is narrow in measures of latency; consequently even a small amount of within-subject variability is likely to influence the rank order of participants and alter the ICC and SEM. When comparing the findings of the current study to those of Bastani [342] and Cacchio [362] it is also worth noting a number of methodological differences. Cacchio's testing was conducted at 20%MVC, the stimulation intensity is not clearly identified, nor the method for determining latency clearly outlined [362]. Bastani and colleagues tested at a stimulator intensity of 120%RMT and identified latency visually, potentially introducing bias [342]. The use of a double cone coil in the current study may have introduced error as described earlier. Some researchers recommend that the shortest latency in a block of stimuli be recorded [363] rather than the average latency over ten MEP's as in the current study. The reliability of the measure may also have been influenced by the method used for determining onset, which was calculated as first point at which EMG activity exceeded

three standard deviations of the Background RMS level. Three standard deviations may have been insensitive when identifying latency and consequently reduce the precision of this measure.

In summary, in keeping with previous research the current study demonstrates that measures of corticomotor excitability of the soleus muscle have good to excellent intra-session reliability in both healthy populations and people with stroke when taken during a 10%MVC. Therefore, these measures can reliably capture immediate (within session) changes in corticomotor excitability in response to rehabilitation interventions in healthy adults and in people with stroke However, this study is one of the first to demonstrate the magnitude within-subject variability in MEP_{AMP} and MEP_{RMS} measures, indicating that even within a single session individuals with stroke need to make a large change in response to an intervention in order to exceed the expected variability in TMS-derived measures of corticomotor excitability.

7.5.4 Inter-session Reliability of TMS-derived Measures during an Isometric Contraction

It was hypothesised that the control group would demonstrate good to excellent inter-session reliability (≥0.6) and the stroke group would demonstrate poor to moderate inter-session reliability (≤0.59) on measures of corticomotor excitability of the soleus muscle during an isometric contraction. This hypothesis was supported for all non-conditioned measures of corticomotor excitability in both groups, except the measure of latency and active motor threshold, which demonstrated good reliability in the stroke group. Inter-session reliability of TMS-derived measures of corticomotor excitability have been more extensively investigated than intra-session reliability. Since the inception of this research a number of new studies investigating some aspect of inter-session reliability in healthy participants [337, 342, 350, 362, 364-367] and a further four studies which investigated some aspect of inter-session reliability in people with stroke [245, 250, 253, 337] have been published.

Active Motor Threshold

The current study reports excellent inter-session reliability of AMT in healthy participants and good reliability in people with stroke, with small within-subject variability and standard error in both groups. Previous studies report inter-session reliability with ICC's from 0.82 [366] to 0.97 [362] and CV of SEM's from 3% [362, 367] to 7% [366] across a range of muscles and time periods (1 day[352, 367] to four weeks [337, 362, 366]) in

healthy participants. In keeping with previous research, motor threshold appears to be a highly reliable measure of corticomotor excitability between sessions in healthy populations.

Two previous studies have investigated aspects of reliability for motor threshold in people with stroke in the lower limb, both reported excellent reliability and small standard error. The current study reports a lower ICC and slightly higher SEM than previously published work. This may reflect differences in the samples, particularly the stroke sample where participants in the current study were more heterogeneous and potentially had a greater level of physical disability than those in Cacchio's [337] or Wheaton's [245] study. Alternatively, the differences in study findings may reflect differences in the method to determine the AMT. In the current study AMT was determined based on five or more out of eight stimuli resulting in a *visually* discernible MEP, in contrast both Wheaton and Cacchio based their determination upon five out of ten MEP's of *at least* 50μV. Notably in Cacchio's study a much higher mean stimulator output (Control μ=62.2 SO%, Stroke μ=84.7 SO%) was utilised to achieve the defined threshold in a more mildly affected group [337] when compared to the current study (Control μ=55.3 SO%, Stroke μ=58.1 SO%). Alternatively this difference may be explained by the experience of the coil operator. Nevertheless, in the current study AMT was found to have good inter-session reliability, small within-subject variability and standard error in people with stroke.

Motor Evoked Potential Amplitude

In keeping with previous research [337, 342, 347, 366, 367], the current study reported excellent reliability for MEP_{AMP} in the control group. Of the three studies which have investigated inter-session reliability of MEP_{AMP} in the lower limb in healthy participants [252, 337, 367], two report excellent reliability [337, 367] whilst Van Hedel and colleagues [252] reported moderate to good inter-session reliability of $MEP_{AMP.}$ However, in their study the duration of time between test and re-test was variable, likely influencing the results.

The inter-session reliability of MEP_{AMP} in people with stroke in the current study was poor, demonstrating that MEP_{AMP} is an unreliable method of measuring lower limb corticomotor excitability in people with stroke between sessions. This finding is in keeping with previously reported research in people with stroke in the lower limb. Cacchio et al. [337]and Wheaton et al. [245] both report similar ICC and CV of SEM's for TA (ICC=0.38, CV of SEM=38%) and quadriceps muscles (ICC=0.21 and 0.54, CV of SEM=64% and 39%) of the more affected side in people with stroke.

Whilst the relative SEM were similar between the control and stroke groups in the current study, comparison of the TE shows that people with stroke had considerably more within-subject variability than control participants in measures of MEP$_{AMP}$. The large within-subject variability in people with stroke may be explained by a number of factors in addition to those described in relation to intra-session reliability above The inter-session CV of TE for MEP$_{AMP}$ in the control group was comparable to that seen within a session, indicating that biological variability and measurement error is fairly stable from one session to another separated by 7 days in healthy participants. The intra-session CV of TE for MEP$_{AMP}$ was also comparable between the groups; in contrast the inter-session CV of TE for MEP$_{AMP}$ in the stroke group was 150%. This finding indicates that there is considerable within-subject variability in MEP$_{AMP}$ measures in people with stroke which is not explained by the measurement method.

The poor inter-session reliability of MEP$_{AMP}$ in people with stroke may be explained by a number of factors. Isometric measures of TMS-derived corticomotor excitability were recorded during a 10%MVC contraction of the plantar flexors. Inter-session reliability testing demonstrated that although people with stroke had good inter-session reliability of MVC, they were less reliable and had greater relative inter-session typical error than controls. This may have introduced variability to the MEP$_{AMP}$ measure specific to people with stroke, as MEP$_{AMP}$ is dependent on the amount of muscle activation and may vary based on fluctuations in %MVC [251, 346, 347]. This may contribute to the increased variability in TMS measures seen in people with stroke. Some evidence for this is provided by the poor inter-session reliability of background RMS in people with stroke. The stroke group had much larger absolute and relative inter-session typical error in Background RMS than the control group and to intra-session values for people with stroke.

Previous research has demonstrated that MEP's obtained during low level voluntary contractions are less variable in healthy participants than those at rest [251, 346, 353, 368, 369], in addition in people with stroke it is often difficult to elicit a MEP at rest. Consequently testing during low level voluntary contraction is recommended when studying people with neurological pathology [353, 363]. However, it is important to note that studies investigating co-ordination in people with stroke identify difficulties sustaining a consistent level of force, particularly at low levels of MVC [254, 255, 370, 371]. Increased within-subject variability in Background RMS might be explained by co-ordination deficits in force grading in people with stroke, although it is not clear why this would be an issue between sessions but not within sessions. Muscle force is graded and sustained through both the recruitment of motor units and the modulation of the rate of

recruitment of motor units [63]. Motor unit recruitment alterations following stroke including; the inability to increase the rate of motor unit recruitment and to vary the rate of motor unit recruitment to meet force requirements [63, 64, 372-374] may result in variation in the background level of EMG activity. Spontaneous firing of motor units at rest and following voluntary contractions have also recently been identified in people with stroke [375, 376], which may further introduce biological variability. The finding of increased within-subject variability in Background RMS in stroke participants may provide support for TMS stimulus triggering based on RMS level in this population, rather than %MVC. Alternatively it may provide support for considering a different motor task which has less within subject variability in this population.

In the current study, the inter-session SEM of MEP$_{AMP}$ was substantial and comparable between groups. Three studies were identified which evaluated the inter-session SEM for MEP$_{AMP}$; one in the lower limb [337] and two in the upper limb [342, 366]. The current study reported a CV of SEM of 38%, which is within the range of previously reported results, however it is considerably more than reported by Cacchio and colleagues who also investigated the corticomotor excitability of a lower limb muscle. The SEM value is influenced by the ICC and the dispersion of the group data (SD). The ICC is comparable between the studies, however the SD of the sample in the current study was much greater (Sample CV=97%) than that of Cacchio's sample (Sample CV=24%). The difference in data dispersion may in part explain the difference in SEM, where a larger SD would result in a larger SEM. The following factors may contribute to the larger SD; Cacchio's participants all underwent an independent familiarisation session prior to reliability testing; this was not the case in the current study, nor in the other studies reviewed. TMS protocols which involves multiple contractions of the target muscle may invoke a neuroplastic effect which influences the stability of measures from the first to second testing session in particular [347, 367], although no systematic bias was identified in the current study. The current study used a double cone coil, whilst Cacchio and colleagues used a circular coil. The double cone coil is designed to provide a more focal stimulation but is known to result in more variable MEP's [346]. Unfortunately Cacchio and colleagues fail to describe the intensity of the stimulation for MEP$_{AMP}$ testing, the number of stimuli used to calculate the MEP$_{AMP}$ or the method of measurement and averaging, making comparison of these methodological aspects difficult, which are all known to influence MEP$_{AMP,}$ [251, 342, 343, 346, 347].

In summary, the current study demonstrates that MEP$_{AMP}$ of the soleus muscle has excellent inter-session reliability in healthy populations; however it has poor inter-session

reliability in people with stroke when taken during a 10%MVC. Much of this poor reliability in MEP$_{AMP}$ in people with stroke can be ascribed to the level of within-subject variability. Variability in MEP$_{AMP}$ in people with stroke might be explained by biological variability including; difficulty grading the appropriate level of force during the task, fluctuations in corticomotor excitability, and the effect of spontaneous firing of motor units and greater desynchronisation of descending action potentials on MEP size. From this study it may be concluded that MEP$_{AMP}$ taken during an isometric contraction of the soleus muscle is an unreliable measure of corticomotor excitability in people with stoke when there are 7 days between testing sessions and is likely unsuitable as a measure of change over time, such as in response to spontaneous recovery or a rehabilitation intervention.

Latency

The present study reported good reliability for latency in both groups. Previous research reports ICC's of between 0.69 [245] and 0.85 [250, 337] in people with stroke, and 0.48 [252] and 0.95 [337] in healthy populations, with most studies reporting reduced ICC's in lower limb muscles [245, 252, 362] compared to upper limb muscles [250, 342, 377]. The latency ICC's of the present study is within the range of previously reported results in both groups. The within-subject variability was low, indicating that the measure is precise.

Conditioned Measures

All conditioned stimuli measures demonstrated poor inter-session, except the ICF RMS which had adequate reliability in the control group. However, the 95% confidence interval in this measure crossed zero, indicating a low level of confidence in the reliability estimate. It should be noted that the raw values for ICI and ICF demonstrated superior inter-session reliability than the normalised values in the control group, with most raw values demonstrating good to excellent inter-session reliability. The purpose of normalisation is to reference the conditioned stimulus (e.g. ICI$_{AMP}$) to the test stimulus (MEP$_{AMP}$) to provide a standardised value of inhibition or facilitation and to account for between subject differences in MEP$_{AMP}$. However, it would appear that the within-subject variability of each component (e.g. ICI$_{AMP}$ and MEP$_{AMP}$) significantly influences the normalised measure (ICI$_{AMP}$/MEP$_{AMP}$) such that it may exceed the true between subject differences in ICI$_{AMP}$. Therefore, the process of normalisation reduces the between-subject data dispersion, as evidenced by a reduction in the sample CV across all conditioned measures in both groups with normalisation. The reduction in the sample dispersion with

normalisation is likely to explain the difference in ICC reliability statistics between raw and normalised values in the control group.

Only two studies were identified which reported inter-session reliability of measures of intra-cortical excitability [366, 378]. Fleming and colleagues evaluated the inter-session reliability of conditioned TMS measures of the FDI in ten healthy adults over three sessions separated by seven days [378]. They reported poor reliability for both ICI and ICF measures (ICC ICI=0.23, ICF=0.01) using a handheld figure of eight coil, with the muscle at rest. However, the authors noted that with the removal of an outlier and the use of navigation, the reliability of ICI improved considerably (ICC=0.93), although no improvements were seen in the reliability of ICF [378]. It is not clear whether this is a spurious finding or highlights the influence of coil movement on ICI but not ICF measures. In contrast, Ngomo and colleagues reported excellent reliability of ICI when taken at rest (4-Day ICC=0.83, CV of SEM=86%, One Month ICC= 0.91, CV of SEM=63%) and adequate reliability when evaluated during a 7.5%MVC contraction in the FDI (4-DAY ICC=0.55, CV of SEM=107%, One Month ICC= -0.43, CV of SEM=159%) [366]. The contrasting findings regarding the reliability of ICI between the studies may be explained by differences in the study protocols. Of note, both the current study and Fleming's study [378] used a randomised order of stimulation (non-conditioned, ICI and ICF). In contrast, Ngomo [366] did not randomise the order. Randomisation of stimuli is likely to have introduced significantly more within-subject variability and may explain the poorer ICC in the current study and Fleming's [378] work in comparison to Ngomo's work[366].

Previous authors have reported significant variability in ICI and ICF as measured by Block CV [379, 380]. Within-subject variability and SEM's in the current study were modest and comparable between the groups. The relative within-subject variability in conditioned measures was analogous to that seen during non-conditioned testing. For example, the CV of TE of MEP_{AMP} was 44% during non-conditioned isometric measures and CV of TE was 59% for ICI_{AMP}/MEP_{AMP} and 47% for ICF_{AMP}/MEP_{AMP}. However, analysis of raw data showed significant within-subject variability in the raw ICI_{AMP} (CV of TE=99%) by comparison to other raw values in the control group (CV of TE 29-48%). The ICI measure may have been influenced by the use of a voluntary contraction during testing which is known to reduce the inhibition seen during ICI compared to when the measures are taken at rest, due to concurrent facilitation [381]. However, at the intensity used for the conditioning stimulus (70%AMT) and the low level of muscle contraction (10%MVC) this is unlikely to have been the case in the current study [382]. The use of a voluntary contraction during the testing protocol was selected in order to enable testing on a diverse

group of people with stroke, not just those with mild motor impairment in whom a MEP could be elicited at rest. In addition, the magnitude of inhibition during ICI may have been influenced by the amplitude of the MEP, as inhibition is greater at larger test MEP amplitudes than used in the current study [383]. Both of these factors may have introduced greater within-subject variability by increasing the relative effect of any absolute error.

Based on the findings of the current study, it can be asserted that TMS-derived measures of intra-cortical excitability of the soleus muscle taken during a 10%MVC contraction have poor inter-session reliability in the both people with stroke and healthy adults. Comparison of normalised and raw values indicates that in healthy people the normalisation process results in a reduction in the sample dispersion, which may in part account for the poor reliability in normalised values.

7.5.5 Inter-session Reliability of TMS-derived Measures during Treadmill Walking

The reliability of TMS derived measures of corticomotor excitability taken during functional tasks has not been previously explored and this study represents the development of a novel protocol for assessing neural plasticity in response to locomotor rehabilitation in people with stroke. Although, the application of TMS during functional movements has been utilised in studies investigating neuroplasticity in response to training in healthy individuals [169, 170] and motor control of functional movements [146, 248, 384, 385]. It was hypothesised that the control and stroke groups would demonstrate good to excellent inter-session reliability (≥0.6) on measures of corticomotor excitability of the soleus muscle during a locomotor task. The hypothesis was supported for the stroke group but not the control group for all non-conditioned measures and rejected for both groups for conditioned measures.

MEP Amplitude

MEP_{AMP} demonstrated poor reliability in the control group and excellent reliability in the stroke group. However, the relative within-subject variability was comparable between the groups, indicating that measurement error and biological variability were similar. Much of the poor reliability in the control group may be attributed to control participants not maintaining their relative rank order on retesting. This is likely to be influenced the sample CV for $MEP_{AMP,}$ which was 66% in the control group, in contrast to the stroke group

where the sample CV was 154%. In this instance, it is likely that the within subject variability exceeded the between subject variability in the control group.

The reliability of the measure and its precision may have been influenced by a number of methodological factors specific to the protocol and TMS derived measurement during walking. Technical error may have introduced during treadmill walking through movement of the coil. The coil was secured using a tightly fitting neoprene cap, Velcro® and an elasticised bandage and then suspended overhead using a system of elasticised straps. There is sinusoidal movement of the head in vertical plane and rotation in the pitch plane during walking, the magnitude of which is dependent on walking speed [386]. Whilst the elasticised straps would have absorbed some of this movement, it is likely that the position of the coil altered during the gait cycle in response to head movement. However, as the stimulus was applied at the same point in the gait cycle the position should have been consistent at the time of stimulation. Movement of the coil may have introduced technical error. Another factor which could have introduced technical error was that the longer participants walked on the treadmill the shorter the duration of the burst of soleus muscle EMG activity during the stance phase became. Presumably, as participants became accustomed to the experimental set up and treadmill versus over ground walking their movement pattern became more refined. As a result, it is possible that the stimulation was applied at a different relative time during the EMG burst, dependent on whether the stimulation was applied early or late in the protocol. This notion is supported by the modest reliability and increased within-subject variability in background RMS in the control group during walking, when compared to the findings in isometric testing which showed excellent inter-session reliability and lower within-subject variability. Refinements to the testing protocol which result in improvements to the timing of stimulation delivery relative to burst duration may result in improvements in MEP_{AMP} reliability and within-subject variability.

Despite the technical challenges of the protocol and the assumed potential for measurement error, it is important to note that the relative within-subject variability in the control group for MEP_{AMP} was consistent across testing situations (CV of TE of MEP_{AMP} Intra-session=47%, Inter-session Isometric=44%, Inter-session gait =49%). This suggests that the compound effect of technical error and biological variability did not differ between testing situations, and indicates that MEP_{AMP} has similar precision in healthy adults whether the measure is taken during an isometric contraction or a functional task. However, it is possible that the relative contribution of biological variability and/or technical error to within-subject variability differed between testing situations.

MEP$_{AMP}$ during walking demonstrated excellent inter-session reliability in the stroke group with modest within-subject variability and standard error. Therefore, in people with stroke, MEP$_{AMP}$ measured during walking has better inter-session reliability, less within-subject variability and better standard error than MEP$_{AMP}$ measured during a low level isometric contraction. Key differences between the measures taken during an isometric contraction and during walking may explain this difference in reliability. Firstly, the stroke sample has a much larger sample dispersion when MEP$_{AMP}$ is recorded during walking (CV of Sample=155%), compared to during an isometric contraction (CV of Sample=51%). It may be asserted that MEP$_{AMP}$ taken during walking is more likely to differentiate deficits in corticomotor excitability than in an isometric contraction in people with stroke. The difference in inter-session reliability between an isometric contraction and walking appears to be related to the within-subject variability in MEP$_{AMP}$. Biological variability and technical error were much less of an influence during walking than during an isometric contraction. There was also a more consistent level of background muscle activity from test to retest in walking compared to during an isometric contraction. This may reflect that walking is a well learnt motor task in this group who were all independently mobilising at least 10 metres with or without aids. Walking is a motor task that this group undertook daily, by comparison to a 10%MVC force matching task which was novel for all participants.

MEP Latency

MEP latency measures demonstrated good reliability in the control group and excellent reliability in the stroke group. Both groups had very low levels of within-subject variability, which was consistent with findings during isometric testing in both groups indicating that the compound effect of technical error and biological variability on latency did not differ between testing situations.

Conditioned Measures

All conditioned measures demonstrated poor test-re-test reliability when normalised to the non-conditioned stimuli in both groups, except the ICF RMS which had good reliability in the control group. When conditioned stimuli measures were analysed as raw values the ICI values demonstrated poor test-retest and the ICF values adequate test-retest reliability in the control group. In contrast the stroke group had excellent test-retest reliability in all conditioned measures when analysed from their raw values. Similar to the non-conditioned measures the within-subject variability was comparable between the groups, indicating that measurement error and biological variability was similar between the

groups for conditioned measures. Collectively the results of reliability testing of conditioned measures during an isometric contraction and during a functional task indicate that based on the protocol of the current study conditioned measures are unreliable between sessions in people with stroke. Further investigation is required to develop a TMS protocol which reliably measures intra-cortical excitability in the lower limb in people with stroke.

In summary, the current study demonstrates that TMS-derived measures of corticomotor excitability of the soleus muscle have good to excellent inter-session reliability in people with stroke when taken during a walking task. Therefore, these measures have the potential to reliably capture long term (between session) changes in corticomotor excitability in response to rehabilitation interventions in people with stroke. However, it is important to note that, this protocol is both technically challenging and maybe arduous for some individuals with stroke. Nevertheless, given the technical demands and limitations of other measures of neural plasticity, the use of TMS to reliably measure long term neuroplastic changes in response to locomotor rehabilitation interventions in a task-specific manner has considerable merit.

7.5.6 Limitations

This study is potentially limited by:

- Failure to identify foot dominance, although the relevance of foot dominance in a hemiplegic population is questionable.
- Failure to describe the history of repeated muscle activity in all participants, and the lesion location in participants with stroke.
- Failure to standardise MEP_{AMP} to maximal motor response (M_{MAX}).
- Triggering based on MVC during isometric contraction, which may not control for the influence of synergists.
- Failure to control caffeine consumption.
- The expertise of the primary researcher in delivering TMS.

7.5.7 Implications for Future Research

The findings of this study indicate that an individual with stroke would need to change their MEP_{AMP} value +/-62% within a session during an isometric contraction to be considered a true change. A change of +/-225% would be required between testing session in a person with stroke when MEP_{AMP} was measured during an isometric

contraction. MEP_{AMP} during treadmill walking is a more sensitive measure of corticomotor excitability between sessions, requiring a +/- 77% change to detect a true change in an individual.

The results of this study indicate that a total sample of 17 participants would be required to detect a modest change in MEP_{AMP} between sessions in people with stroke using TMS applied during treadmill walking. Previous studies investigating corticomotor excitability changes in people with stroke have reported moderate to large effect sizes in threshold and map size during isometric contraction in response to locomotor rehabilitation [173, 176] suggesting that a modest effect size is achievable. However, the expected magnitude of change in response to rehabilitation has yet to be established.

As discussed earlier, further studies could address whether inter-session reliability of TMS derived measures of corticomotor excitability in people with stroke can be improved by triggering based on a level of EMG RMS rather than %MVC. This may reduce the level of biological variability present in the measure.

Comparison of normalised and raw ICI and ICF values indicated that in healthy people the normalisation process resulted in a reduction in the sample dispersion, which may in part have accounted for the poor reliability in normalised values. This may provide support for the concept that intra-cortical excitability measures should be obtained by using a stimulus which; results in a specified test MEP amplitude, is relative to its threshold intensity or is normalised to the M_{MAX} [387]. This requires further investigation. However, this is unlikely to be feasible in people with stroke who have varying levels of corticomotor excitability may limit the size of evoked potentials.

There is considerable scope to further refine the treadmill walking testing procedure, and room for technical advances, particularly in the stabilisation of the TMS coil during functional movement. This refinement in the testing procedure would likely improve the inter-session reliability of TMS-derived measures taken during treadmill walking in people with stroke and healthy participants.

In addition to the greater reliability of TMS-derived measures of corticomotor excitability when taken during treadmill walking, assessment during a functional task in people with stroke has the potential to broaden the application of this tool to people with significant deficits who are usually excluded from TMS based studies. A MEP is more likely to be identified in a person moderately or severely affected by stroke during a functional motor

task than at rest or in an isometric contraction. Inclusion of such people would reduce the selection bias which is associated with the measurement tool.

7.6 Summary

TMS has previously been used as a marker of neural plasticity following locomotor rehabilitation in people with stroke [173, 174, 176]. However, studies using standard TMS protocols suggest that TMS is an unreliable method of measuring neural plasticity over time, in the lower limb [245, 337]. In the current study, a repeated measures cross-sectional design, with 7 days between sessions, was used to evaluate the reliability of TMS-derived measures of corticomotor excitability of the soleus muscle. Measures were obtained in a standard protocol during an isometric contraction and in a novel protocol during treadmill walking in healthy people and people with stroke. The main findings of the study indicate that;

- Non-conditioned TMS-derived measures of corticomotor excitability of the soleus muscle demonstrate excellent intra-session and inter-session reliability in healthy participants when evaluated during an isometric contraction.
- Conditioned TMS-derived measures of corticomotor excitability of the soleus muscle demonstrate excellent inter-session reliability in healthy participants when evaluated during an isometric contraction
- Conditioned and non-conditioned TMS-derived measures of corticomotor excitability of the soleus muscle demonstrate poor inter-session reliability in healthy participants when evaluated during walking
- Non-conditioned TMS-derived measures of corticomotor excitability of the soleus muscle demonstrate excellent intra-session reliability in people with stroke when evaluated during an isometric contraction
- Non-conditioned TMS-derived measures of corticomotor excitability of the soleus muscle demonstrate poor inter-session reliability in people with stroke when evaluated during an isometric contraction
- Non-conditioned TMS-derived measures of cortical excitability of the soleus muscle demonstrate excellent inter-session reliability in people with stroke when evaluated during walking.
- Conditioned TMS-derived measures of cortical excitability of the soleus muscle demonstrate poor inter-session reliability in people with stroke when evaluated during an isometric contraction and during walking

The findings of this study indicate that conditioned measures of corticomotor excitability have questionable reliability when presented as a normalised value in people with stroke. TMS-derived measures of cortical excitability evaluated during an isometric contraction

are a suitable measure of immediate intra-session neuroplastic changes in people with stroke. However, researchers who aim to measure long term neuroplastic changes in people with stroke should consider TMS measures taken during a relevant functional motor task.

SECTION THREE

STRENGTH FOR TASK TRAINING:

A PILOT STUDY

Chapter 8   Pilot Study

8.1 Prologue

The first section of this thesis described the preclinical phase of the STT intervention development. This process was grounded in the MRC recommendations [388] for the development of complex interventions in that it identified and reviewed the relevant evidence base and neuroscientific literature, and undertook a process of defining the key features of the intervention, consultation with key stakeholders and the development of resources to facilitate the STT implementation. This section of the thesis focuses on the pilot testing of the STT intervention

8.2 Introduction

Pilot studies (also known as feasibility studies) are strongly recommended in the literature describing the development and evaluation of complex interventions [22, 388, 389]. In addition, pilot studies are specifically recommended in the development of rehabilitation interventions [15, 390]. A pilot study is a powerful tools in the development of an intervention and considerable information can be gleaned about the intervention under investigation, which may promote its refinement prior to implementation in a larger trial [22, 390]. Pilot studies can address intervention adherence, fidelity, acceptability to health professionals and participants and to a lesser extent safety. It is important to note that the intent of a pilot study is not to establish intervention efficacy; the treatment effect is usually considered only using descriptive analysis, acknowledging the inappropriateness of statistical testing.

In addition to information about the intervention, pilot studies can enable the assessment of the feasibility of study processes to aid in development of the study protocol for the planned evaluation of the intervention. In particular, pilot studies can enable researchers to evaluate recruitment and retention rates, the influence of eligibility criteria, randomisation and blinding procedures, the success and suitability of the study data collection methods and tools, and the personnel, time and equipment resources required to implement the study design [23, 391]. Whilst the scope of questions which can be

addressed in a pilot trial are wide, it is essential that the aims of any pilot trial are explicitly stated and that the criteria for feasibility are specified [23, 392].

Whilst many publications in relation to pilot studies focus on quantitative research methods, a number of authors recommend consideration of mixed methods during pilot trials [23, 389, 393]. Mixed methods refers to the integration of quantitative and qualitative methods into one scientific enquiry. This approach involves the integration of both methods at various phases of the research process, and specifically during analysis and interpretation of results, such that the two data sets provide a fuller description of the processes under investigation.

In the context of a pilot study, qualitative methods have the potential to provide data in relation to; reasons for engagement with the research process and perceptions of that process, elucidation of errors, unblinding, treatment adherence and negative responses to the intervention [394]. By eliciting participant and health professional perceptions about barriers and facilitators to engagement, and the identification of participants perceptions about the key features of the intervention, qualitative methods have the potential to be particularly powerful [393, 394]. By highlighting promoters and detractors to intervention acceptability, qualitative methods can be used to refine interventions and provide indications as to how an interventions effectiveness is best promoted in clinical practice [394].

Intervention acceptability should be a key consideration in the development of rehabilitation interventions. One of the most significant challenges to the success of any exercise rehabilitation programme, regardless of its scientific merit, is whether participants perceive it to be beneficial to them and whether the programme is tailored in such a way to allow individuals to engage [395-397]. Therefore consideration of the participant's perspective was considered crucial in the development of the STT intervention and drove the selection of a mixed methods approach to piloting.

The aim of this pilot study was to establish the feasibility, acceptability and safety of the STT intervention and to evaluate feasibility of the research protocol for testing the intervention in a randomized controlled trial.

8.3 Study Aims and Objectives

8.3.1 Planned Main Study

The intended aim of the planned main study, a randomised controlled trial, is to investigate whether Strength for Task Training (STT) is an effective locomotor rehabilitation intervention in people following stroke by examining its effect on participation, activity, impairment and neural plasticity.

The primary objective of the planned main study is to determine the immediate effect of STT on gait speed in post-stroke survivors. Secondary objectives of the planned main study are to;

> (1) determine and compare the immediate effect of STT, Progressive Resisted Strength Training (PRST), Task-specific training (TST) & Usual Care Control (UCC) interventions on improving muscle strength in post-stroke survivors
>
> (2) determine and compare the immediate effect of STT, PRST, TST & UCC interventions on improving locomotor abilities in post-stroke survivors
>
> (3) determine and compare the immediate effects of STT, PRST and TST on participation and HRQoL in post-stroke survivors;
>
> (4) explore the effects of STT, PRST, TST and UCC on neural plasticity post-stroke survivors;
>
> (5) determine the relationship between changes in measures of neural plasticity and changes in measures of locomotor ability in response to locomotor rehabilitation.

The primary hypothesis is that STT will increase gait speed more than UCC, PRST or TST alone.

8.3.2 Pilot Study

The aim of this pilot study was to establish the feasibility, acceptability and safety of the STT intervention and to evaluate feasibility of the research protocol of the planned Main Study for testing the intervention in a randomized controlled trial. Therefore, the specific aims of this pilot study were to;

(1) Establish the feasibility of the sampling and recruitment strategy,

(2) Establish the integrity of the trial protocol,

(3) Establish the feasibility, acceptability and safety of the STT intervention,

(4) Establish the magnitude of the difference and variance estimates of the outcome measures.

It was determined that the future main study protocol would be considered feasible if:

1. Twenty participants were recruited to the pilot study within a two month timeframe.
2. Data completeness exceeded 95%.
3. Intervention adherence exceeded 80%.
4. Intervention fidelity exceeded 80%.
5. The participants and the physiotherapists deemed the interventions acceptable.
6. Adverse events were at or below rates previously described for people with stroke when exercising.
7. Any protocol deviations could be addressed with minor alterations to the protocol and its implementation.

8.4 Pilot Study Method

8.4.1 Study design and setting

This mixed method study involved a randomised, controlled, single blind pilot trial design. The intent was to mimic the planned main study protocol as closely as possible in order to establish its feasibility. Therefore, the pilot study included a group of twenty people aged over 18 years who had a single stroke three to nine months previously. Participants were assigned to one of four intervention groups: STT, PRST, TST or UCC. Outcome measures of participation, activity, impairment and neural plasticity were conducted prior to and immediately following a twelve week intervention period. Semi-structured interviews with both participants and physiotherapists written feedback were used to explore the feasibility and acceptability of the intervention, and specific markers were used to evaluate the sampling and recruitment strategy, the safety of the intervention and the integrity of the trial protocol.

This study was undertaken at the Health & Rehabilitation Research Institute of AUT University, Auckland, NZ. The recruitment phases were initiated in July 2010 and June 2011, and the assessment and intervention phases were conducted from July 2011 to October 2011.

8.4.2 Sample

Sample Size

As this study was a pilot study, a sample size of twenty (5 per group) was utilised. This sample size allowed one cycle of each of the intervention arms to be conducted. This number was considered sufficient to establish the integrity of the research protocol and consider the effect of the intervention on the outcomes of interest [390, 398].

Inclusion Criteria

Individuals were considered eligible for the study if they;

    a. were aged over 18 years
    b. had experienced a single disabling stroke 3-9 months prior.
    c. were able to walk 10m with or without aid and with or without standby assistance
    d. had a gait speed of 0.05 to 1.2m/s at entry to the study

The decision to include only those who were more than 3 months post-stroke was made to ensure participants were likely to be medically stable and have persistent walking problems. In addition, most recovery occurs within the first year after stroke, therefore the present study sort to maximise overall recovery by increasing participation and overall physical activity during this crucial window of time [399].

Exclusion Criteria

Individuals were excluded from the study if;

    a. their behaviour would interfere with participation in a group setting, as noted during initial assessment (e.g., agitation, aggression)
    b. they had a significant cognitive deficit (Mini-Mental State Examination Score ≤23)
    c. they were unable to follow a 1-step English verbal command
    d. they were unable to give informed consent
    e. they were medically unsuitable in the opinion of the screening physiotherapist, their General Practitioner or medical specialist
    f. they were participating in another study that, in the opinion of the investigator, may affect the results of this study or add significantly to the participant's burden
    g. they had excessive pain in any joint that could limit participation
    h. they had another condition that could impact results (e.g., substance abuse, significant mental illnesses such as major depression)

i. they had any contra-indications to TMS, including pacemaker, artificial heart valves, other metal implants, pregnancy, skull abnormalities, history of seizures or epilepsy or taking medications that may lower seizure threshold

j. they had any cautions or contra-indications to blood sampling for BDNF measurement including fear of needles, reception of a blood product or blood transfusion within the 4 weeks prior to the study commencing, taking medications which adversely affect blood coagulation (e.g., Warfarin).

8.4.3 Ethical and Cultural Considerations

Ethical approval for the study was obtained from the NZ Health and Disability Ethics Committee (Northern X) in July 2010 (see Appendix I). This trial was registered with the Australian and NZ Clinical Trials register, registration number ACTRN12610000460000 (refer to Appendix J). Amendments to the study were approved by the ethics committee in September 2010 and September 2011 (refer to Appendix J and Appendix L respectively and Section 8.5.1 for a summary of these protocol changes).

This study was non-ethnic specific in that it neither specifically targeted nor excluded participants based on ethnicity. In acknowledgement of the disparities in post-stroke disability, dependence and HRQoL between Māori and non- Māori and to ensure that the study supported participation for Māori, a detailed consultation process with Māori was undertaken as part of the wider research programme.

8.4.4 Study Procedure

This pilot study involved blinded baseline assessment of measures of neural plasticity, impairment, activity, participation and HRQoL. Following baseline assessment each participant was assigned using pseudo-randomisation (minimisation) to either STT, PRST, TST or UCC groups. The intervention period lasted 12 weeks. All participants were then re-assessed on relevant outcome measures. Semi-structured interviews were conducted with participants in the post-intervention phase to explore the feasibility and acceptability of the intervention. Refer to Figure 8-1 for an outline of the study flow.
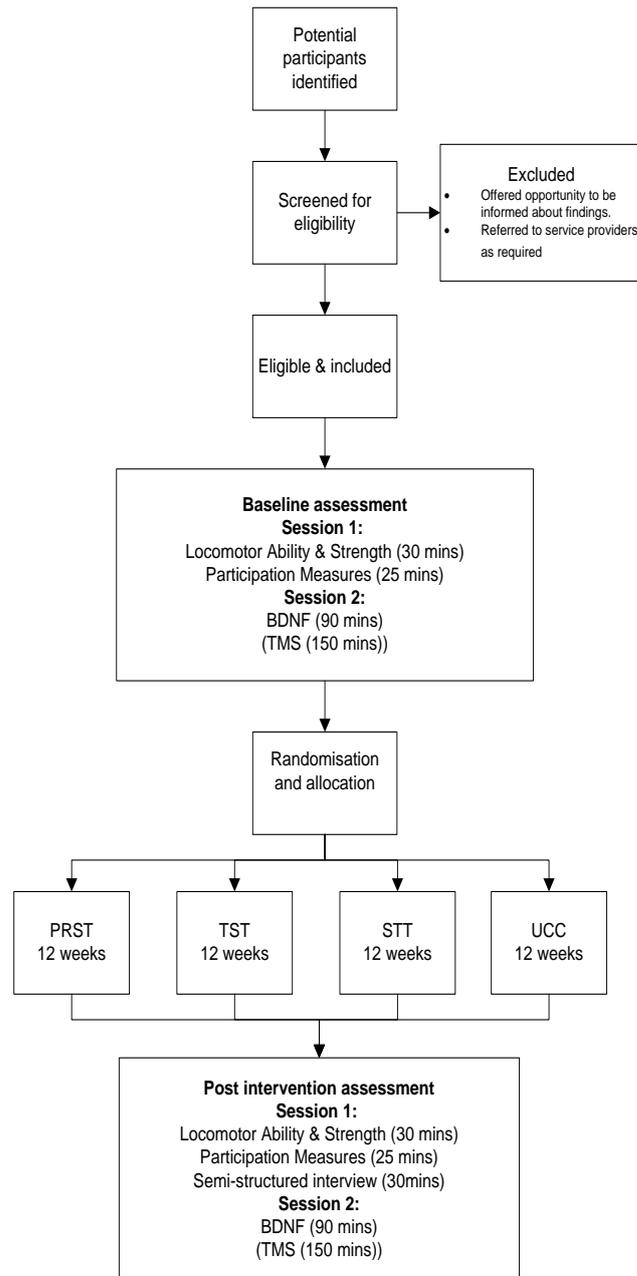
Figure 8-1 Study Flow

Recruitment Strategy

Participants were recruited to the study from local hospital stroke clinics, local neurological physiotherapy clinics, the Stroke Foundation and through local media advertising. Potential participants recruited via local hospital stroke clinics, local

neurological physiotherapy clinics and the Stroke Foundation were identified by staff at these locality organisations and handed or posted a study information sheet (refer to Appendix M). Those interested in participating then either contacted the research team or gave permission for the organisation to give their details to the research team so they could be contacted. Potential participants who responded to local media advertising contacted the study team independently and were given an information sheet and offered the opportunity to have the study verbally explained and ask questions.

It was estimated that approximately 1000 stroke survivors attended the hospital stroke clinics annually [400]. In addition, because the study intended to recruit participants 3 to 9 months post-stroke, it was possible to recruit from participants already on file within these clinics; an additional approximately 500 stroke survivors. It was estimated that 50% of stroke patients from these clinics would present with persistent gait problem [30, 401] (n=750) and that 20% of eligible stroke survivors would agree to participate [34]. It was therefore estimated that recruitment from the local hospital clinics alone would yield approximately 13 participants over a two month recruitment period. The success of the recruitment strategy is discussed in Section 8.5.1.

Screening

Potential participants were screened via telephone by a trained research physiotherapist. The physiotherapist sought basic information from the person in regards to their stroke, locomotor disability and medical history relevant to the inclusion and exclusion criteria. They also specifically screened for cognitive deficits using the MMSE, for contraindications to TMS using the TMS Screening Questionnaire (refer to Appendix H) and to exercise based on absolute contraindications to exercise including; a history of recent myocardial infarction, uncontrolled cardiac conditions such as angina, arrhythmias, heart failure or severe aortic stenosis, uncontrolled hypertension, uncontrolled metabolic disorders, significant musculoskeletal pain in the lower limbs which limited basic ADL's, major depression or psychiatric illness or acute infection [104, 402]. Relative contraindications to exercise were recorded for handover to the treating physiotherapist. Where potential participants could not readily answer questions over the telephone a face-to-face meeting was offered. All potential participants had the parameters and risks of the study explained and were offered the opportunity to ask questions about the study during the screening process. Potential participants who were deemed likely eligible were asked for permission to inform their General Practitioner or Medical Specialist of their intention to be considered for the study. The purpose of this letter was to offer General Practitioners the

opportunity to identify potential concerns regarding the participants undertaking the study.

Baseline Assessment

Following screening, potential participants were offered an appointment time for informed consent and baseline assessment. All assessments were individually administered according to standardised procedures by blinded, trained research physiotherapists over two sessions.

In the first assessment session demographic characteristics of participants including age, sex, ethnicity, clinical characteristics of stroke, medical history, current medications and cautions and contra-indications to TMS, BDNF and exercise were gathered. Outcome measures of impairment and activity were conducted in a randomised order, as were measures of participation and HRQoL. In the second testing session measures of neural plasticity were gathered. Refer to section 8.4.5 for a detailed explanation of each measure.

Randomisation

Following baseline assessment participants were pseudo-randomised to one of the four groups (STT, PRST, TST, UCC) using minimisation. Minimisation involves dynamic allocation, where the first participant in the minimisation protocol is randomly allocated and each subsequent participant is allocated based on the balance of relevant factors among the groups. Minimisation is considered methodologically equivalent to true randomisation the Consolidated Standards of Reporting Trials Group (CONSORT) [77], yet has the advantage of reducing the risk of unmatched groups, particularly when the sample size is small [403]. The minimisation protocol was carried out using the Minim programme [404] and was designed to assign participants based on their age and comfortable walking speed, as these were considered important prognostic factors for response to treatment intervention[405]. The categories for age were;

<55 years
55-64 years
65-74 years
75-84 years
≥ 85 years

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and for walking speed were;

<0.4 m/s
0.4-0.79 m/s
0.8-1.19 m/s
≥1.19 m/s

All participants were assigned within the same session by a blinded researcher not involved in other aspects of the trial to ensure that no selection bias was introduced. All participants were blinded to the study hypothesis and were only informed whether they had been allocated to a rehabilitation or control group.

Intervention Phase

Participants who were allocated to the STT, PRST or TST groups were scheduled to attend a group based exercise programme for twelve weeks, whilst the UCC group kept a record of any physical rehabilitation or organised exercise they engaged in during the intervention phase. Refer to Section 8.4.7 for details of each intervention.

Post-intervention Assessment

In the week following the end of the intervention phase all outcome measures conducted in the baseline assessment were re-administered according to the same standardised procedures as described in the Baseline Assessment. Post-intervention semi-structured interviews were also conducted which focused on the acceptability of the respective intervention (STT, TST or PRST). The interview structure is outlined in Section 8.4.6.

8.4.5 Outcome Measures

Neural Plasticity

Measures of neural plasticity including BDNF and TMS were conducted as described in Chapter 6 and Chapter 7. The reliability and validity of these measures in discussed in these chapters also.

Impairment

Leg Muscle Strength (1-RM)

A 1-RM is the maximum weight a person can move through a prescribed range of motion once. Using a modified (supine) leg press machine a 1-RM was established using Dowson's protocol [406]. Participants were positioned on the supine leg press machine in a standardised position with the knee and hip at 90°. Participants completed one set of 10 repetitions at a modest load bilaterally to allow for familiarisation. The participant's less affected leg was then secured via a supporting strap and they then completed five repetitions with their more affected leg at a sub-maximal load. Once single repetitions of heavier loads began, a rest period of one to five minutes between repetitions was provided. The load was increased incrementally to ensure 1-RM was reached within five attempts [407]. This protocol has been used extensively in our laboratory in various populations, including people with stroke[55]. The inter-session reliability of 1-RM testing is excellent in older adults [408, 409] and the inter-session reliability of other forms of strength testing is excellent in people with stroke [410-412]. The 1-RM of the more affected leg was normalised to the participants' body weight to provide a functionally relevant description of weakness [413, 414].

Activity

30 Second Chair Stand Test (30sCST)

The 30sCST evaluates a person's ability to stand and sit as quickly as possible in 30 seconds, and is regarded as an indirect measure of lower limb strength and functional mobility status [415]. The test takes approximately one minute to complete and begins with the participant sitting with their arms crossed over their chest in a straight backed chair without arms (seat height approximately 43 cm). The chair was positioned against wall or heavy object to prevent it from moving during the test. The participant was instructed to rise to a full stand and return back to a fully seated position after the signal "go" was given. They were encouraged to complete as many full stands as possible within a 30 s time limit. The assessor demonstrated the test for the participant and allowed a practice trial of 1 to 2 repetitions to ensure correct form. One 30-second trial was performed and the total number of stands executed correctly within 30 seconds was recorded. The inter-session reliability of the 30s Chair Stand Test in people with stroke is excellent [416].

Comfortable Paced Walking Speed (CWS)

CWS is a measure of the participant's walking velocity at a self-paced comfortable speed. CWS reflects impaired locomotor function in people with stroke and is a reliable [417-419], valid and sensitive measure of recovery of locomotor function after stroke [420, 421, 422]. CWS has also been shown to differentiate between people who are housebound and those who access the community [29]. The test took approximately two minutes to complete and was conducted on a marked walkway with a stopwatch. The participant was asked to walk at their comfortable pace along a 10 m walkway whilst the assessor recorded the length of time it took the participant to walk the middle 6 m. Three trials were conducted and the average walking speed determined [327].

Fast Paced Walking Speed (FWS)

Fastest Walking Speed test is a measure of the participant's walking velocity at a self-paced fast speed. Data collection was as described for Comfortable Paced Walking Speed except that the participant was asked to walk at their fastest possible speed. Inter-session reliability of fast paced walking speed is excellent in people with stroke and the measure has been validated against other measures of locomotor function and endurance [421].

Step Test

The Step Test is a measure of dynamic balance which takes approximately 30 seconds to complete. The participant was asked to stand 3 cm in front of a 7.5 cm step and instructed to step one foot up and down onto the step as many times as possible in 15 seconds; the number of full steps on each leg was recorded. The test was then repeated on the other leg to give a score for both the left and right legs. This measure has excellent inter-session reliability and is sensitive to change in people with stroke [6]. It has been validated against other measures of locomotor function [421].

Stair Ascent/Descent

Stair ascent/descent is a measure of stair climbing ability. A standard staircase with steps measuring 16 cm high, 28 cm deep, and a rise angle of 60° and a sturdy rail on either side was used to quantify the time taken to ascend and descend stairs. The participant stood at the bottom of the first step and was instructed to climb the ten steps as quickly as possible, placing only one foot on each step. Timing began when the leading foot left the ground and was stopped when the trailing foot contacted the last step. The procedure was repeated for stair descent. The length of time to ascend 10 steps and descend 10 steps was recorded

and presented as an average time per step. This measure has excellent inter-session reliability and has been validated against other measures of locomotor function [421].

Self-Efficacy, Health Related Quality of Life and Participation

Activities-Specific Balance Confidence Questionnaire (ABC)

The Activities-Specific Balance Confidence Questionnaire is an interviewer administered self-report questionnaire of balance self-efficacy focusing on confidence in the maintenance of balance during sixteen common locomotor activities. The participant was asked to rate their confidence performing each activity on a 0-100 percent scale, with 0 percent representing no confidence and 100 percent representing complete confidence. An overall score was calculated by averaging the scores for all the items. The ABC has excellent inter-session reliability, high internal consistency [423]. Balance self-efficacy is more strongly associated with participation than measures of physical activity such as balance, walking speed or endurance [424].

Stroke Impact Scale (SIS)

The SIS is a self-report questionnaire which evaluates the impact of stroke on health and life, including quality of life [425] Eight domains (strength , hand function, activities of daily living, mobility, emotion, memory/thinking and participation/life role) were evaluated using 59 items. Each item was rated on a 5-point Likert scale in terms of the difficulty the person experienced in completing the item, and a summative score was generated for each domain. An additional question on stroke recovery asked the participant to rate on a scale from 0-100 how much they felt they had recovered from their stroke. The questionnaire took approximately 15 minutes to complete. The inter-session reliability of SIS domains range from 0.70 to 0.92, except for emotion domain (0.57) [426] and the questionnaire has published MCID and MDC scores [427]

Subjective Index of Physical and Social Outcome (SIPSO)

The SIPSO is a self-report questionnaire of physical and social integration following stroke which takes approximately seven minutes to complete. The SIPSO contains 10 items which are summed into two subscales of physical and social integration or a total score. The SIPSO has excellent inter-session reliability [428].

8.4.6 Participant Interviews

This mixed methods study utilised qualitative interviews to evaluate the acceptability of the interventions for participants. The study adopted a descriptive approach to qualitative analysis using semi-structured interviews post-intervention [429]. This approach allowed for flexibility in response to the person being interviewed and the interview context in order to develop a deeper understanding of factors which influenced intervention acceptability for the person with stroke, and allowed exploration of the complexities of engagement in the intervention from the perspective of the individual [429]. The initial interview guide was developed by the primary researcher (NS) in consultation with the wider research team.

Post-intervention interviews were focused on the participant's response to the intervention including the acceptability of the intervention, the individual cost-benefit of participating in the respective intervention and any perceived benefits/impact. It was the intention of the interviewer to keep the interviews as open-ended as possible; however, prompts were used if necessary to gain a deeper understanding of the participants' experience. The questions illustrated below serve as examples of the kinds of prompts used to encourage the participant to talk about their experiences and opinions. These prompts were used as required.

- How has the rehabilitation programme affected you?

- What have you liked about the rehabilitation programme?

- What have you not liked about the rehabilitation programme?

- Do you have any suggestions for improvements?

- Do you think that the effort you put into the programme was worth the benefits you got out of it?

- You identified XXX as rehabilitation goals before starting the programme; can you tell me a bit about how well you have progressed towards those goals?

- What would stop you from participating in this rehabilitation programme?

- What would help you to participate in this rehabilitation programme?

- How did the intensity of the programme help or hinder your participation?

- What sort of people would you recommend /not recommend the programme to?

All interviews were conducted by trained qualitative researchers experienced in working with people with neurological pathologies. Interviewers were not involved in other aspects of the study. Interviews lasted from 20 to 45 minutes and were audio-taped and transcribed verbatim. Significant others or other persons the participant wished to have present at the interview in a support role were welcomed.

8.4.7 Interventions

Usual Care Control

The UCC group continued to receive standard rehabilitation through public and private health care services; no effort was made to influence the type or amount of rehabilitation these participants received. It should be noted that in the context of the NZ healthcare system people with stroke are likely to be receiving minimal or no active rehabilitation at 3-9 months post-stroke [430]. The frequency and duration of any physical rehabilitation interventions and/or organised exercise that participants in the UCC group undertook was recorded using a monthly calendar. Participants were taught how to use the calendar system by an unblinded member of the study team and the calendars were returned monthly. Participants who did not return their monthly calendars were reminded via telephone and post, as required. Participants were also telephoned if their returned calendar required clarification.

Intervention Groups

People who were allocated to the STT, PRST or TST groups were scheduled to attend a group based exercise programme three times per week for one hour. The intervention period lasted for twelve weeks and was undertaken between 27/06/2011 and 16/09/2011, with a total planned volume of rehabilitation of 36 hours. Please refer to the section describing the Chapter 4 for details of the STT intervention rationale, development process and the intervention parameters. The PRST and TST groups completed the single mode of the STT intervention; the PRST group received only the strength training component of the STT programme and the TST group received only the task-specific training component of the intervention. The dose and attention was matched across the groups.

Physiotherapist Training

Local NZ registered physiotherapists with at least five years post-graduate experience were recruited to act as treating physiotherapists for the programme. Each physiotherapist had experience in stroke and older adults' rehabilitation. Therapy assistants were recruited from the third year students of the undergraduate physiotherapy degree at Auckland University of Technology.

Each treating physiotherapist and therapy assistant had a two hour, one-on-one training session with the lead investigator in which the underpinning principles of the intervention were introduced, and the content and logistics of the intervention discussed. The session covered;

- The theoretical basis of the intervention
- The programme content and structure
- The specifics of each exercise and the relevant progressions
- Logistics of a single training session, including the timing and transitions between exercises
- Orientation to the gym environment and equipment
- Methods for monitoring participants and documenting individual and group responses
- Managing risks including emergency protocols and adverse events reporting
- Maintaining the research trial integrity including blinding

After this session, physiotherapists spent self-directed time working through the respective intervention manual and documentation; if required they had another meeting with the principal investigator. Please refer to Appendix A for an example of a training manual.

Clinical Supervision

Each treating physiotherapist had an unblinded member of the study team attend their sessions at least twice during the first two weeks of the programme and on at least one other occasion during the intervention period. These study team members were also NZ registered physiotherapists who were familiar with the theoretical basis and practical application of the intervention programmes. They also provided telephone and email support to the treating physiotherapist for the duration of the study. The purpose of this support was to provide clinical supervision to the physiotherapist, to facilitate problem

solving and clinical reasoning in relation to the intervention and to answer any questions the treating physiotherapist may have with the intention of maintaining a high level of intervention fidelity.

Documentation

Each treating physiotherapist received a memory stick with electronic versions of all relevant study documentation saved on it. These included;

- Participant biographies outlining demographic information, medical history, precautions to exercise, medications, impairment and locomotor ability assessment results and rehabilitation goals for each participant.
- Participant intervention planning and documentation Master Form which acted as a clinical record for each contact (Refer to Section 4.6.2)
- Adverse Event Reporting Form
- Weekly Feedback Form

Clinical record

For each participant, the treating physiotherapist planned the ensuing intervention session and printed a paper copy of the clinical record to hand to the participant at the beginning of the session. The participant and the physiotherapist recorded any amendments to the planned intervention made during the actual session. After the session the physiotherapist updated the electronic record to reflect the actual intervention undertaken. A copy of each participant's intervention recording sheet for each session was saved on the memory stick, such that an electronic record of all 36 training sessions for each participant was maintained.

Physiotherapist Feedback

Each week the treating physiotherapist reflected on the programme and provided written feedback to the study team related to logistics, environment and equipment, specifics of the exercises, group dynamics, participant response to the programme and any other relevant information. This feedback was emailed to an unblinded member of the study team for review.

Adverse Events

Adverse events were defined as an event which caused the participant to seek attention from a health professional, or limited their activities of daily living for at least two days.

Treating physiotherapists were required to complete an adverse events form which included participant details, a description of the event, its outcome, details of any medical care required and any relationship between the adverse event and the rehabilitation programme. They then emailed the form to an unblinded member of the study team for review. The intent was that if there was any indication that the research was harmful to participants, it would be stopped and the situation reviewed (including consultation with relevant parties and bodies) before making a decision about whether to continue. Serious adverse events were to be reported to the funding body and ethics committee.

8.4.8 Study Monitoring

In order to address the study objectives related to feasibility, a number of study parameters were recorded.

Recruitment

During the recruitment phase the number of considered, screened, and eligible potential participants was recorded.

Data Completeness

Actual versus expected data records received were evaluated for all pre and post intervention outcome measures and all intervention documentation.

Intervention Adherence

The number of participants who completed the programme and the number of attended sessions was recorded.

Intervention Fidelity

Intervention fidelity refers to the extent to which the parameters of the interventions were delivered as they were intended [431]. Fidelity with the prescribed parameters of exercise was evaluated by review of intervention documentation which recorded progressions, volume and intensity of exercise. Participants were deemed to have achieved the required volume of prescribed exercise if they completed the specified minimum number of sets in the session. For the TST and PRST groups, this equated to two sets of each of the seven exercises and in the STT group one set of each of the seven combined exercises. Participants were deemed to have achieved the required intensity of prescribed exercise if they completed the exercise at the specified intensity for that session of the programme.

Fidelity with the requirement to progress exercise was evaluated based on the total number of progressions made in the TST component and the percentage change in load from baseline in PRST component.

Intervention safety

Adverse events were recorded and analysed for severity, relationship to the intervention, healthcare requirements and outcome.

Protocol Changes and Deviations

Any changes to, or deviations from, the described protocol were recorded.

8.4.9 Data Processing

Quantitative Data

All feasibility data were descriptively analysed (number, mean, standard deviation, minimum and maximum as relevant). All outcome measures were descriptively analysed (number, mean, standard deviation, minimum and maximum). Mean differences between pre- and post-intervention data were calculated, along with their 95% confidence intervals. As this was a pilot study designed to assess the feasibility of the study protocol and not powered to determine clinical efficacy there was no interferential statistical assessment.

Qualitative Data

Qualitative descriptive data from the interviews and physiotherapists' weekly feedback summaries were analysed using descriptive content analysis. The intent of the qualitative descriptive data analysis was to provide a rich description of participants' experiences and opinions of the intervention acceptability, rather than an interpretation. However, it is acknowledged that description cannot be free from interpretation [429].

Interviews were listened to verbatim and then interview transcripts were read and re-read. A loose coding framework was initially manually applied to sentences or phrases. Subsequently transcripts were transferred into NVivo (version 10) [432] and re-coded. Comparison between the initial manual coding and the electronic coding was then undertaken. In order to gain an understanding of the relationships among codes, a number of other strategies were utilised to analyse the data. These included constant comparison within and across codes and data sources, and the use of memos to record details of the

codes and to keep track of initial thoughts about the data and any hypothesised interactions among codes. Where relevant, codes were then grouped to themes and negative case analysis was used to identify data which was contradictory or dissonant with the proposed theme; this was an iterative process. Two coded transcripts were sent to a second researcher (KM –secondary supervisor) to ensure consistency of interpretation, and two meetings were held to discuss the interpretation of the data with the aim of reaching consensus on thematic development. Different iterations of the thematic model were discussed and revised with the wider research team to ensure suggested relationships between themes and intervention acceptability represented were consistent with the agreed interpretation of data. For the purposes of data representation, illustrative quotes were selected that corroborated the data.

Integration of Quantitative and Qualitative Data Sets

True mixed methods studies involve the integration of both quantitative and qualitative data sets to facilitate the interpretation of the results [433, 434]. This mixed methods study utilised a process of triangulation to gain a more complete picture of the data. For the purposes of triangulation quantitative data was defined as all numerical data related to: recruitment, intervention adherence and fidelity and participant outcome. Qualitative data was defined as all non-numerical data provided by the study team and locality organisation staff, the clinical records, participants post-intervention interviews and physiotherapists weekly written feedback.

The process of triangulation involved listing the findings from each data set (quantitative and qualitative) and comparing the information obtained. The intent was to identify if the data sets demonstrated agreement with one another, offered complementary information to each other to draw a more complete picture or appeared contradictory. This process was undertaken for each aspect of the study protocol under investigation: recruitment, intervention adherence, intervention fidelity, intervention safety and data completeness. Primacy was given to the quantitative data set in all aspects of the study protocol, except intervention acceptability. The qualitative data set was expected to support (converge) or add detail and/or explain (complementary) the quantitative data set or highlight errors or omissions in the study protocol or its implementation (dissonant) [394].

8.5 Results

The results section focuses on the feasibility aspects of the study related to the study protocol integrity and the intervention, and the study outcomes for the respective groups.

To facilitate interpretation of the study results in each section, relevant quantitative results are presented first, followed by the results of triangulation of quantitative and qualitative data sources. Triangulation includes summarisation of the main findings of each data set; along with acknowledgement of the data source and the results of the triangulation of the data sets (refer to Section 8.4.9 for a summary of the triangulation process).The full qualitative descriptive analysis of the participant and physiotherapist interviews is presented in the latter part of Section 8.5.2.

8.5.1 Study Protocol Integrity

The study protocol integrity is evaluated with respect to any protocol changes made, the flow of potential participants through the recruitment and screening process, the flow of participants through the study, the sample characteristics, data completeness and any deviations from the planned protocol.

Protocol Changes

Three protocol changes were made during the process of this pilot study.

Changes to the recruitment strategy (August 2010)

In response to poor recruitment to the initial recruitment phase (refer to Section 8.5.1 for a summary of recruitment outcomes) the inclusion and exclusion criteria and the recruitment methods for the study were reviewed by the study team and locality organisation staff and an amendment to the study protocol was undertaken. The intent of this amendment was to broaden the reach of the recruitment strategy and to facilitate the engagement of people with stroke in the research process. The changes involved removing the 9 month cut-off period post-stroke to include, all people aged over 18 years with a single, first stroke; more than 3 months post stroke at the start of the intervention. A more comprehensive follow up of potential participants was also undertaken to ensure those with communication, mood and cognitive impairments had the potential to engage with the research study if they desired. Please refer to Appendix K for a copy of the ethics amendment approval.

Changes to the interpretation of the exclusion criteria (April 2011)

Review of the first recruitment phase highlighted a potential flaw in the pilot study protocol in relation to the interpretation of the exclusion criteria. Notably, in the main study, measures of neural plasticity were intended to be undertaken in a subset (20%) of

the total sample as an exploratory analysis to investigate the mechanisms associated with recovery of function as the result of interventions. However the wording of the exclusion criteria in the pilot study was such that they may have been interpreted as exclusions for participation in the entire study protocol rather than in the relevant measure of neural plasticity. Hence, a review of the interpretation of the exclusion criteria was undertaken by the study team and the approving ethics committee was consulted. It was agreed that the exclusion criteria *i* and *j* would only be applied to the undertaking of the relevant measure of neural plasticity (TMS and BDNF) to ensure participant safety in regards to those measures, and would not be interpreted as a reason for exclusion from the entire study. Please refer to section 8.4.2 for details of these exclusion criteria.

The addition of post-intervention interviews with the physiotherapists (September 2011)

In order to augment the data provided by the treating physiotherapists in their weekly feedback summaries (refer to Section 8.4.7) an amendment to the protocol was undertaken to include a post-intervention interviews with the treating physiotherapists. This one hour interview was conducted by the same trained qualitative researchers who conducted the post intervention interviews with the stroke participants. Interviews were audio-taped and transcribed verbatim, and focused on the barriers and facilitators to participation and the feasibility, acceptability and value of the interventions. The questions illustrated below serve as examples of the kinds of prompts used to encourage the physiotherapists to talk about their experiences and opinions. These prompts were used as required:

- What do you think stops people with stroke from participating in rehabilitation?
- What helps people with stroke to participate in rehabilitation?
- What have you liked about the rehabilitation programme?
- Please comment on the parameters of the programme (group staffing, group dynamics, type of exercises, intensity, progressions/modifications, duration, frequency, instructions, documentation and reporting methods, safety, staff training, equipment, environment, professional support etc)
- Did the effect of the programme vary?
- Did some participants benefit more or less?
- Are there any ideas or concepts from the rehabilitation programme you will integrate into your clinical practice?

Please refer to Appendix L for a copy of the ethics amendment.

In summary, three planned protocol changes were made during the course of the study. Please refer to Protocol Deviations below for a description of any unplanned deviations from the planned protocol.

Recruitment

The first measure of the feasibility of the main study protocol was that 20 participants would be recruited to the study within a two month timeframe.

Recruitment Phase 1

The first phase of recruitment was initiated from June 29th to August 28th 2010. Of the 115 people considered in the two month timeframe 17 people (14%) expressed an interest in being involved in the study, and of those two were eligible (2%). Refer to Figure 8-2 for a summary to recruitment and screening and Table 8-1 for details of the source of potential participants Table 8-3 for a summary of the reasons for ineligibility.
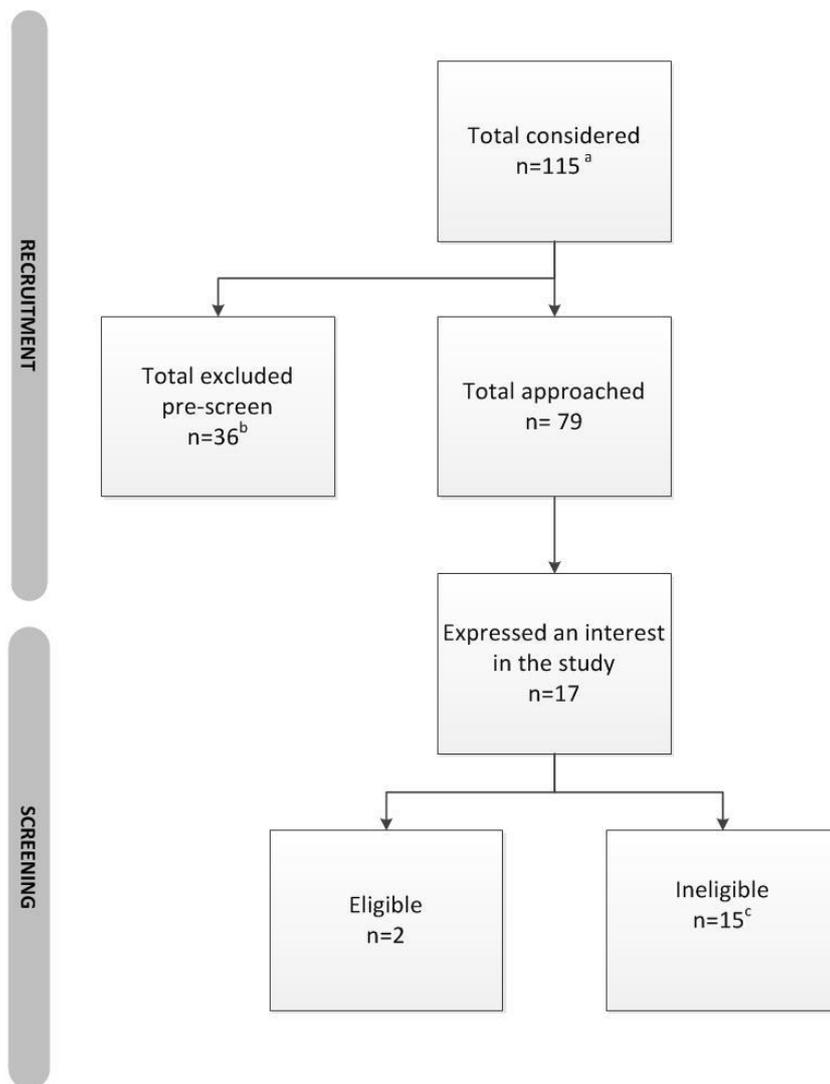
Note: [a] Refer to Table 8-1, [b] Refer to Table 8-2, [c] Refer to Table 8-3

Figure 8-2 Recruitment Phase 1

Table 8-1 Recruitment Phase 1 - Considered Participants Referral Source

Source	Number	Percentage
Hospital Stroke Services	112	97
Local Physiotherapy Clinics	3	3
Stroke Foundation	0	0
Responded to Advertisement	0	0

Table 8-1 indicates that the majority of potential participants identified in the first phase of recruitment were sourced from hospital stroke services.

Table 8-2 Recruitment Phase 1 – Reason for Pre-screen Exclusion

Reason	Number	Percentage
Not stroke	6	17
Not first stroke	11	31
No deficit in walking	6	17
Unable to walk	3	8
Medical condition contraindicates	10	28

Table 8-2 highlights the primary reasons for pre-screen exclusion were that potential participants had experienced more than one stroke, that the eventual diagnosis was not stroke or that the person did not experience an ongoing problem with walking as a result of their stroke.

Table 8-3 Recruitment Phase 1 - Reason for Ineligibility

Reason	Number	Percentage
Not first stroke	3	20
Involved in other research	2	13
No deficit walking/deficit resolved	4	27
Medical condition contraindicates	5	33
Unwilling to participate	1	1

In the first phase of recruitment potential participants were excluded on screening due to reporting a medical condition which contraindicated participation, having no ongoing walking deficit or having experienced more than one stroke.

Recruitment Phase 2

The second recruitment phase utilising the amended recruitment strategy (refer to Section 8.5.1) and inclusion criteria was initiated in June 2011. Of the 97 people considered 37 (38%) people expressed an interest in being involved in the study, and of those 18 were eligible (19%). Recruitment was completed within one month. The total cohort for the study was made up of two people recruited in the first recruitment phase and eighteen in the second. Please refer to Figure 8-3.
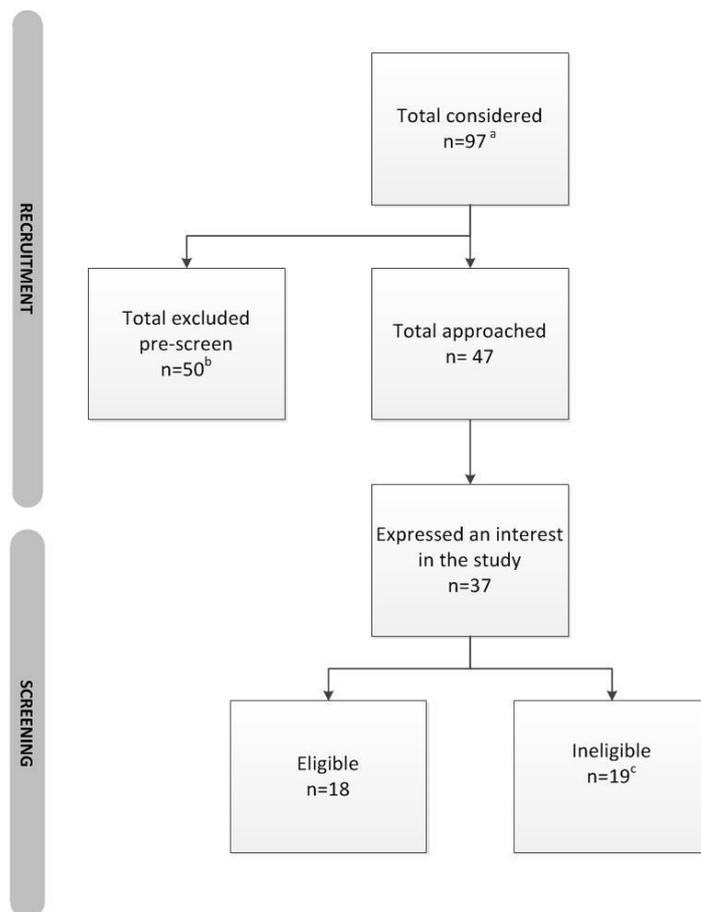
Note: [a] Refer to Table 8-4, [b] Refer to Table 8-5, [c] Refer to Table 8-6

Figure 8-3 Recruitment Phase 2

Table 8-4 Recruitment Phase 2 - Considered Participants Referral Source

Reason	Number	Percentage
Hospital Stroke Services	56	58
Local Physiotherapy Clinics	12	12
Stroke Foundation	14	14
Responded to Advertisement	15	15

Table 8-4 indicates that in the second phase of recruitment the majority of potential participants were sourced from hospital stroke services, although potential participants were also sourced from local physiotherapy clinics, the Stroke Foundation and local media advertising.

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Table 8-5 Recruitment Phase 2 – Reason for Pre-screen Exclusion

Source	Number	Percentage
Not stroke	11	22
Not first stroke	9	18
No deficit in walking	13	26
Unable to walk	8	16
Medical condition contraindicates	9	18

In the second phase of recruitment potential participants were excluded at pre-screen for a variety of reasons.

Table 8-6 Recruitment Phase 2 - Reason for Ineligibility

Reason	Number	Percentage
Not first stroke	3	16
Involved in other research	1	5
No deficit walking/deficit resolved	1	5
Medical condition contraindicates	6	32
Unwilling to participate	8	42

Table 8-6 indicates that in the second phase of recruitment the main reasons for ineligibility were unwillingness to participate or having a medical condition which contraindicated participation.

Data Integration

In addition to the quantitative recruitment data, qualitative data was obtained from locality staff and study team staff feedback, and physiotherapist and participant post-intervention interviews. Table 8-7 triangulates quantitative and qualitative data in relation to recruitment and screening of participants. Triangulation indicates that all data was complementary, where qualitative data provides detail and depth to the quantitative data.

Table 8-7 Recruitment – Data Integration

Quantitative Findings	Qualitative Findings	Triangulation
Pre-screening of people post-stroke by locality staff excludes many people. (Recruitment data)	People with stroke are unlikely to respond to written letters. (Locality staff feedback)	Complementary
Few people 3-9 months post-stroke approached about the study expressed an interest in participating. (Recruitment data) Many people 3-9 months post-stroke who were interested were ineligible. (Recruitment data)	People volunteered for this study for a variety of reasons: few other options for rehabilitation, take any free rehabilitation on offer, altruism, at the behest of significant others, to please research staff, to get out of the house/have something to do. (Participant interviews/ Physiotherapist interviews)	Complementary
Many people who were more than 3 months post-stroke who were interested in participating were eligible (Recruitment data)	Greater liaison with locality staff and more community networking results in greater numbers of approached participants being interested. (Study team feedback)	Complementary

In summary, following amendment to the inclusion criteria and recruitment strategy, recruitment was achieved within a two month timeframe.

Participant Flow

Figure 8-4 describes the flow of the participants through the study. Twenty participants were randomised. One participant discontinued the PRST intervention but completed post-intervention assessment and one participant in the PRST group withdrew from the study and was lost to follow up.
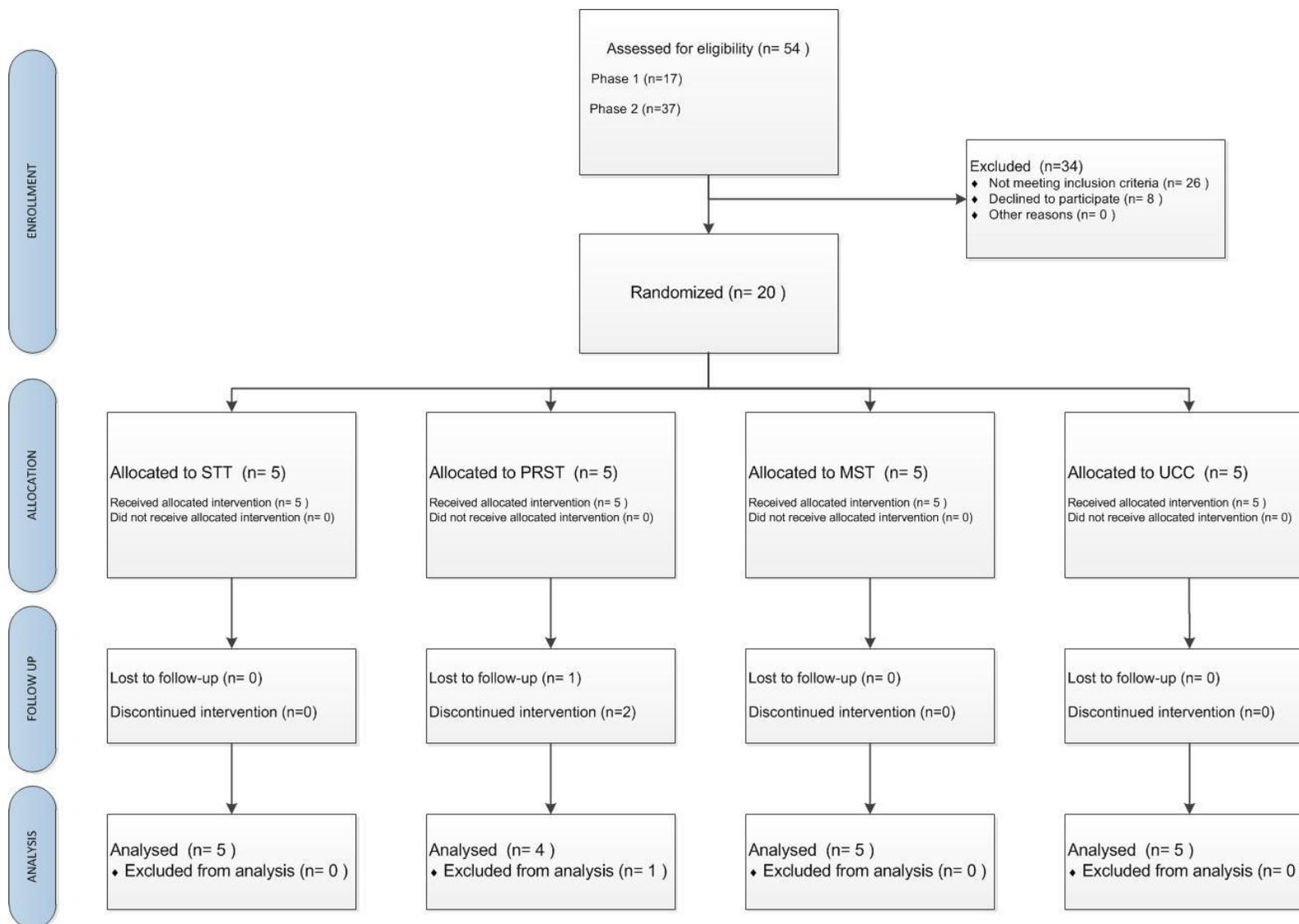
Figure 8-4 Participant Flow

Sample Characteristics

Table 8-8 presents pertinent information about the study sample including; age, sex, walking speed, assistive device use, time since stroke and hemiplegia. The mean age of the sample was 71 years, with a wide range of age from 50 to 92 years. There were eleven male and nine female participants. Walking speed provides an indication of the level of physical disability of the participants; the mean walking speed was 0.74 m/s, with a broad range of walking speed from 0.12 to 1.33 m/s. Participants were on average 42.85 months post-stroke, with a range from 5 to 152 months; indicating that participants who were in the sub-acute and chronic phases following stroke were recruited for the study. Thirteen participants presented with left hemiplegia and seven with right hemiplegia. The intervention groups appeared balanced with respect to age, gender, hemiplegia and time since stroke. The mean walking speed of the TST group appeared slightly lower than the other groups.

Table 8-8 Sample Characteristics

		Group (n=20)	STT (n=5)	PRST (n=5)	TST (n=5)	UCC (n=5)
Age	Mean (SD)	71.15 (12.74)	70.4 (15.60)	73.80 (13.05)	66.80 (12.09)	73.60 (13.05)
	Range	50 - 92	50 - 90	56-92	51 - 81	57 - 85
Sex	Male	11	2	3	3	3
	Female	9	3	2	2	2
Walking Speed	Mean (SD)	0.74 (0.41)	0.83 (0.46)	0.79 (0.42)	0.58 (0.42)	0.75 (0.43)
	Range	0.12 - 1.33	0.14 - 1.33	0.14 - 1.29	0.12 - 1.04	0.23 - 1.22
Assistive Devices	Gutter frame	2	0	1	1	0
	Quad Cane	1	1	0	0	0
	Straight Cane	10	2	3	2	3
	None	7	2	1	2	2
Time since stroke	Mean (SD)	42.85 (41.34)	34.00 (27.27)	34.20 (24.31)	41.20 (53.27)	62.00 (57.38)
	Range	5 - 152	5 - 68	13 - 72	6 - 132	11 - 152
Hemiplegia	Left	13	3	3	3	4
	Right	7	2	2	2	1
Ethnicity	NZ European	17	4	4	3	5
	Pacifica	2	0	1	1	0
	Other	1	1	0	1	0

Note: SD= Standard deviation

Data Completeness

The results of data completeness refer to the actual data obtained compared to that expected, for the assessment and intervention phases of the study. Table 8-9 presents these data for all outcome measures at Baseline assessment. 98% of data was complete with only the TMS data and a single measure of stair climbing missing in one participant.

Assessment

Table 8-9 Baseline Assessment-Actual vs. expected Data Set

	TMS	BDNF	1-RM	30sCST	CWS	FWS	Step	Stairs	ABC	SIS	SIPSO	INTERVIEW
Expected	4	15	20	20	20	20	20	20	20	20	20	20
Actual	0	15	20	20	20	20	20	19[a]	20	20	20	20

[a] Participant unable to be assessed

Table 8-10 provide details for reasons for exclusion from TMS This tables illustrate that a large number of participants were excluded from TMS testing for a variety of reasons, primarily due to contraindications to TMS testing.

Table 8-10 Reasons for Exclusion from TMS

Reason	Number
Medication	6
Metal	3
Frailty	3
Refused	2
Epilepsy	1
History of Traumatic Brain Injury	1
Known to have no Soleus MEP	1

Three people were excluded from the BDNF measurement as they took Warfarin, One participant refused and another was unable to tolerate the testing due to insufficient cardiovascular fitness. . Participants were primarily excluded from BDNF measurement due to taking Warfarin.

Table 8-11 provides details of the post-intervention assessment, indicating 97% data completeness. Loss of data relates to one participants withdrawal from the study, one participant who was unwilling to complete a 1-RM assessment and one who was unable to complete the BDNF assessment due to back pain.

Table 8-11 Post-intervention Assessment: Actual vs. Expected Data Set

	TMS	BDNF	1-RM	30sCST	CWS	FWS	Step Test	Stairs	ABC	SIS	SIPSO	INTERVIEW
Expected	4	15	20	20	20	20	20	20	20	20	20	20
Actual[a]	0	13[b]	18[c]	19	19	19	19	19	19	19	19	19

[a] One participant withdrawn

[b] One participant unable due to back pain in response to unrelated physical activity in the previous week.

[c] One participant refused to participate.

Intervention

Table 8-12 indicates the data completeness of intervention records for each week of the study for each group. For each group the data set was expected to be five. Data completeness was 100% for intervention records and 97% for the UCC calendar records.

Table 8-12 Intervention records – Actual Data Set

Week	1	2	3	4	5	6	7	8	9	10	11	12
STT	5	5	5	5	5	5	5	5	5	5	5	5
TST	5	5	5	5	5	5	5	5	5	5	5	5
PRST	5	5	5	5	5	5	5	5	5	5	5	5
UCC	4[a]	5	5	5	5	5	5	5	5	5	5	5

[a] Weeks entry partially completed for one participant

Data Integration

Qualitative data in relation to data completeness for assessment was sourced from study team feedback and participant and physiotherapists post-intervention interviews. Triangulation of data as described in Table 8-13 indicates that all data was complementary.

Table 8-13 Data Completeness Assessment – Data Integration

Quantitative Findings	Qualitative Findings	Triangulation
Data completeness for both baseline and post-intervention measures was excellent (except TMS). (Study documentation)		
Many participants were excluded from measures of neural plasticity, especially TMS. (Study documentation)	Participants were too fatigued to complete both TMS and BDNF testing in one session. (Study team feedback)	Complementary
Two assessment sessions is insufficient to gather all the baseline and post-intervention data. (Study documentation)		

Table 8-14 triangulates quantitative and qualitative data for data completeness during the intervention phase. Triangulation indicates that there was a discrepancy between quantitative and qualitative data sets. The quantitative data indicated that data completeness for all the intervention groups was excellent, whereas qualitative data from the physiotherapists' interviews calls into question the accuracy of the intervention clinical records.

Table 8-14 Data Completeness-Intervention – Data Integration

Quantitative Findings	Qualitative Findings	Triangulation
Data completeness for all intervention groups was excellent. (Clinical records)	Completing the intervention recording form whilst training was a challenge for some participants. (Physiotherapists interview)	Dissonant
	People with cognitive and perceptual impairments found filling in the intervention record particularly difficult. (Physiotherapists interview)	
Data completeness for UCC group was excellent (Clinical records)	Some participants did not accurately or completely record their training. (Physiotherapists interview)	
	In the STT group the Physiotherapist completed the recording of RPE, repetitions completed and task difficulty. (Physiotherapists interview)	

Protocol Deviations

Deviations from the final study protocol are described in the table below. There were six deviations from the study protocol; one in the recruitment and screening phase, one at baseline assessment and four in the intervention phase. The primary researcher was unblinded to the allocation of three participants.

Table 8-15 Protocol Deviations

Stage of research process	Protocol deviation	Description
Recruitment and Screening	Failure to follow the inclusion criteria	Two participants were enrolled in the study whose comfortable walking speed exceeded 1.2m/s.
Baseline Assessment	Incomplete data set	TMS data was not collected from the four participants who were eligible for TMS
Intervention Phase	Failure to report all adverse events	Physiotherapists failed to report adverse events which they deemed unrelated to the intervention.
Intervention Phase	Addition to the interventions	Physiotherapists requested to stage informal social gatherings to celebrate the half-way and end-point of the intervention. This request was approved and all groups hosted celebrations.
Intervention Phase	Unblinding	The primary researcher was unblinded to intervention group allocation in two participants by seeing them in the hallways of the research institute during the intervention phase.
Intervention Phase	Unblinding	The primary researcher was unblinded to group allocation of a participant in the PRST group when discussing an adverse event with an unblinded study researcher.

8.5.2 Intervention

The intervention was evaluated with reference to adherence, fidelity acceptability and safety. Adherence, fidelity and safety data were collated by analysing intervention clinical records and adverse events reporting forms, while acceptability to both participants and physiotherapists was determined by qualitative descriptive analysis of post-intervention interviews.

Adherence

Adherence was evaluated based on session attendance. The attendance by group over the duration of the programme is reported below in Table 8-16 and the reasons for non-attendance outlined in Table 8-17.

Table 8-16 Session Attendance

	Weeks 1-3	Weeks 4-6	Weeks 7-9	Weeks 10-12	TOTAL
STT	98%	98%	96%	100%	98%
TST	93%	87%	100%	98%	94%
PRST	93%	73%	47%	58%	68%

Table 8-17 Reasons for Non-attendance

Reason	Number of lost sessions	Percentage of total sessions	Percentage of lost sessions	Number of participants
Related Adverse Event	24	4%	34%	2
Unrelated Medical	36	7%	51%	6
Planned Absence	10	2%	14%	5
Total	70	13%	100%	10

Attendance levels were consistently high in the STT and TST groups. In contrast, in the PRST group one participant discontinued with the intervention in Week 5 due to an injury sustained during the intervention (Refer to Safety) and another participant discontinued with the programme in Week 5, and later withdrew from the study, due to an unrelated medical illness (Refer to Safety). A third participant also had slightly reduced attendance. The majority of non-attendance related to unrelated medical problems and related adverse events. Planned absences such as for holidays and personal appointments across all groups accounted for a loss of 2% of total sessions.

Data Integration

Table 8-18 triangulates quantitative and qualitative data in relation to adherence to the intervention, and indicates that all data was complementary. Qualitative data from the participant and physiotherapists interviews provides considerable depth to explain the lower adherence in the PRST group.

Table 8-18 Adherence – Data Integration

Quantitative Findings	Qualitative Findings	Triangulation
Adherence was excellent in the TST and STT groups. (Clinical records) Adherence was not excellent in the PRST group. (Clinical records) Adherence was influenced by two withdrawals in the PRST group(Clinical records) Lost sessions were due to unrelated medical problems, adverse events and to a lesser degree to planned absences. (Clinical records)	For two participants in PRST group the reasons for reduced adherence were multifactorial and included; • having external motivators for engagement with the research study • feeling like the social aspects of the group did not support their involvement • injury/ negative symptoms in response to exercise • other life events • the time commitment • being unable to identify how the intervention might be of value to them (Participant interviews/Physiotherapist interview)	Complementary

Fidelity

Treatment fidelity was evaluated based on whether training was conducted within the specified training parameters in relation to volume, intensity and progression of exercise.

Volume

Volume was evaluated based on the whether participants achieved the specified volume of training for each exercise, at each training session. Figure 8-5 represents the average percentage of exercises conducted at, above or below the minimum specified volume for each group, over the duration of the programme. The specified minimum volume of exercises was two sets for the PRST and TST groups and one set for the STT group.
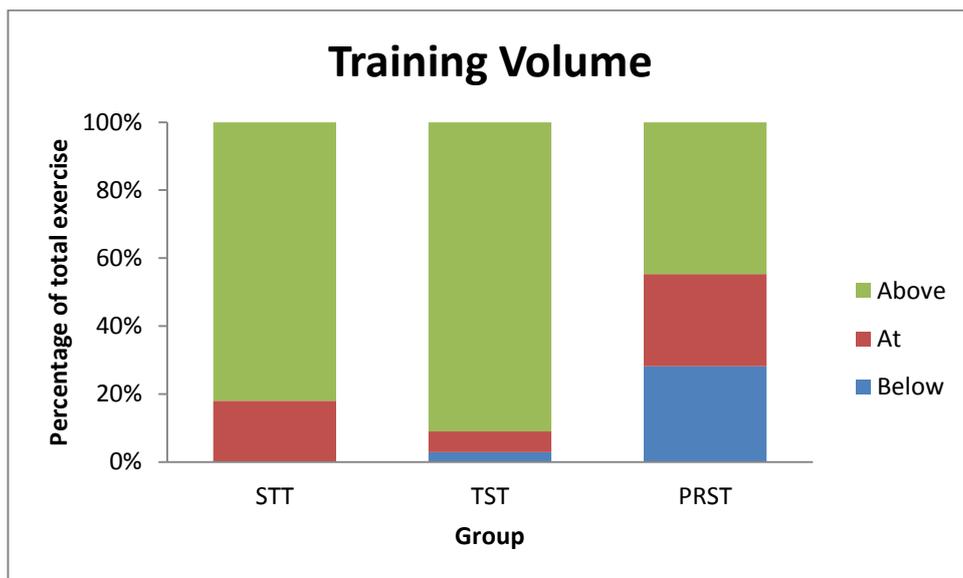
Figure 8-5 Training Volume

Figure 8-5 indicates that the STT and TST groups did an equivalent amount of training above the specified training volume, where most participants completed three sets of each exercise in the TST group and two sets in the STT group. In contrast in the PRST group 28% of exercises were conducted below the specified volume (two sets).

Table 8-19 triangulates quantitative and qualitative data for intervention fidelity in relation to the volume of exercise. Qualitative data was sourced from review of clinical record written documentation and physiotherapists' post-intervention interviews. Triangulation indicates that whilst most of the data was complementary, the qualitative data from the physiotherapist interviews calls into question the accuracy of some of the quantitative data in the STT and PRST groups. The qualitative data also adds depth to explain participant specific reasons for reduced volume in the PRST group.

Table 8-19 Intervention Fidelity- Volume – Data Integration

Quantitative Findings	Qualitative Findings	Triangulation
Exercise volume was at or above the specified level in more than 80% of exercises in the STT group (100%) and TST (97%). (Clinical records)	Some participants had the volume of their exercise modified to account for negative symptoms and adverse events. (Clinical record notes/ Physiotherapists interviews)	Complementary
	In the STT group the physiotherapist recorded the amount of exercise completed in the clinical record, not the participant. (Physiotherapist interview)	Complementary
In the STT and TST groups participants consistently achieved more than the minimum prescribed number of repetitions. (Clinical records)	In the PRST group there were a variety of participant specific reasons for not attaining the specified volume including; • requiring prompting to transition between stations in a timely manner • having to wait for assistance to set up the machines and weights • experiencing postural hypotension during exercises and requiring frequent rests (Physiotherapist interview/Clinical record notes)	Complementary
Exercise volume was at or above the specified level 72% of the time in the PRST group. (Clinical Record)		
In the PRST group four of the five participants failed to achieve the minimum volume of exercise at least some of the time. (Clinical Record)	The volume noted in the clinical record did not always reflect the actual amount of exercise completed in the PRST group, with one participant failing to record his second set of exercises. (Physiotherapist interview)	Dissonant

Intensity

Figure 8-6 indicates the percentage of training conducted at, above or below the specified repetition maximum, whilst

Figure 8-7 indicates the percentage of training conducted at, above or below the specified RPE on the final repetition, by group.
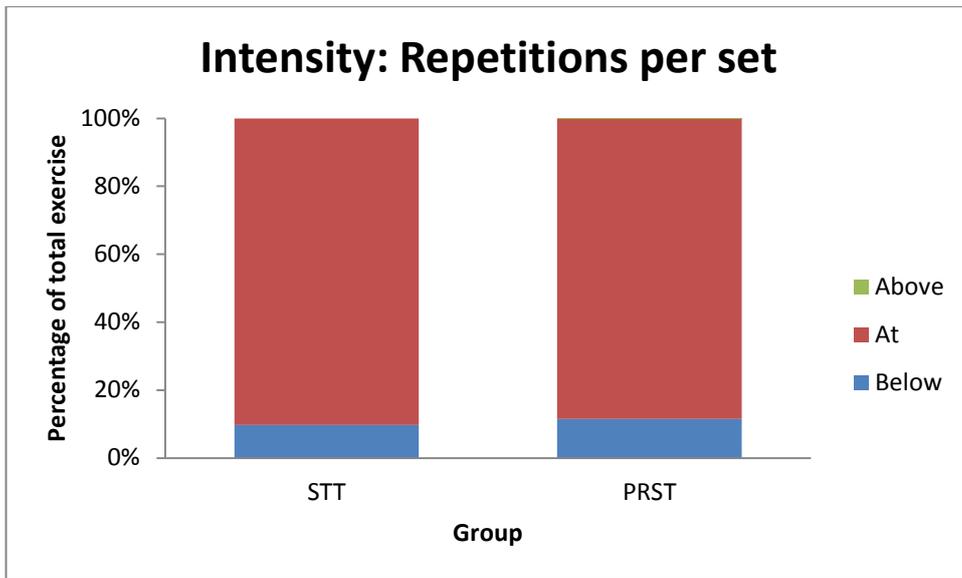
Figure 8-6 Intensity –Repetitions per Set
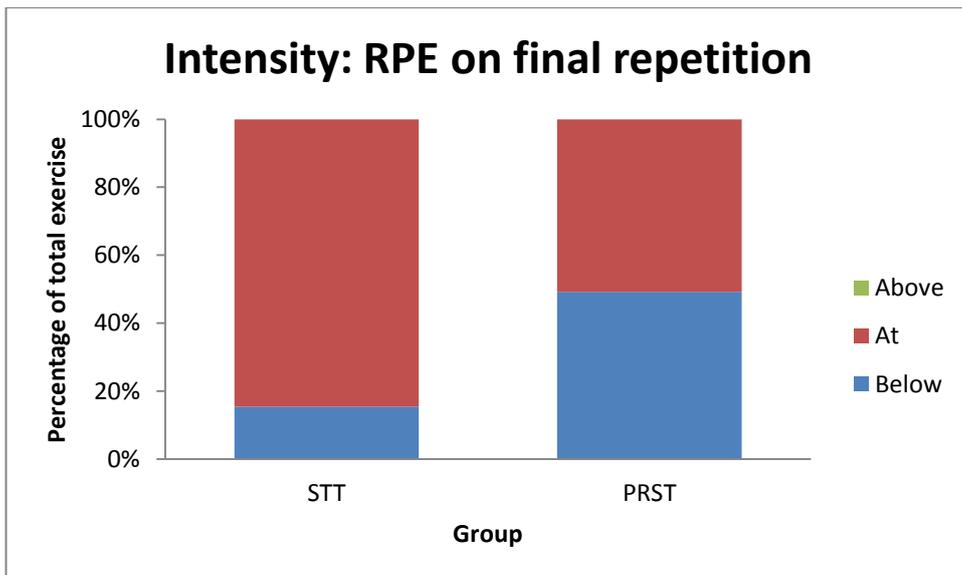
Figure 8-7 Intensity - RPE on the Final Repetition

Figure 8-6 and

Figure 8-7 indicate that the STT and PRST groups achieved a similar percentage of total training at the specified RM with an average of 89% and 87% of exercise conducted at the specified RM respectively. In contrast the RPE on the final repetition was not achieved in

15% of training in the STT group and 49% of the exercises in the PRST group, indicating that more exercises were conducted below the specified intensity in the PRST group compared to the STT group. In both groups, participants failed to reach the specified RPE during the dorsiflexion exercise.

In the task-specific training component exercise intensity was set based on the perceived difficulty of each task, such that each participant aimed to be working at a specified level of difficulty, which increased as the programme progressed. Figure 8-8 indicates the percentage of exercises conducted at, above or below the specified task difficulty in the STT and TST groups. In contrast to the TST group, the STT group had 55% of exercises conducted above the specified task difficulty. This was primarily due to the majority of STT participants working above the specified task difficulty in the middle phase of the programme (Weeks 3-8).
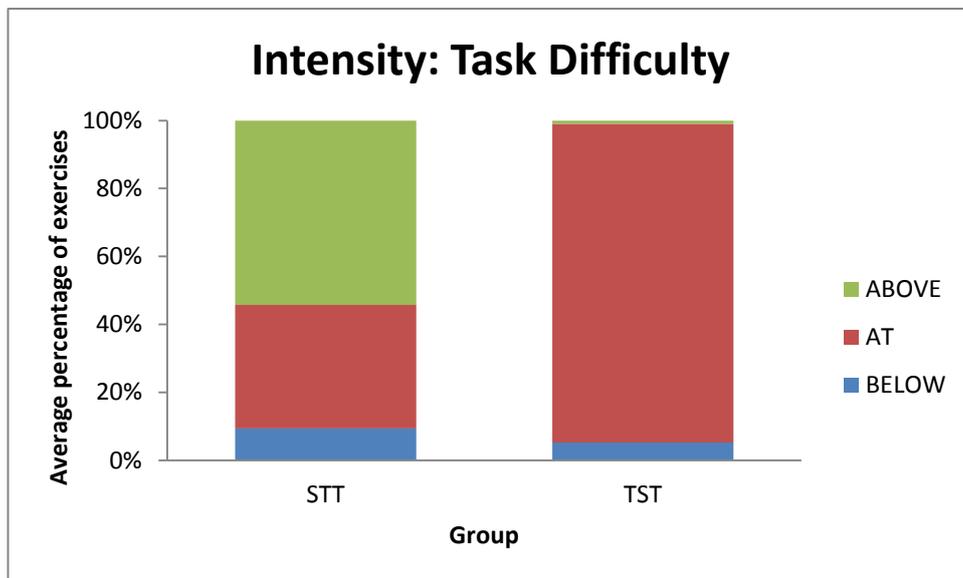
Figure 8-8 Intensity - Task Difficulty

Qualitative data in relation to the achievement of intervention intensity was sourced from participant and physiotherapists' post-intervention interviews and review of clinical record written documentation. Table 8-20 triangulates quantitative and qualitative data in relation to the intensity of exercise. Triangulation indicates that whilst most of the data represented agreement or complementary information between the data sets; there are some discrepancies between the data sets. In particular, participants' descriptions of intensity of training in the STT group did not correlate with intensity data recorded in the clinical record, and although the STT physiotherapist described feeling well prepared to

carry out the intervention the clinical records indicate that she did not carry out the intervention as specified in the training manual.

Table 8-20 Intervention fidelity- Intensity – Data Integration

Quantitative Findings	Qualitative Findings	Triangulation
Fidelity was achieved in relation to the RM in both the STT and PRST groups. (Clinical Record)	Participants in all groups described working hard. (Participant interviews)	Convergent
Intensity fell below the required RM at points of progression. The fidelity for the required RPE for the final repetition was achieved in the STT group but not the PRST group.	Participants in the PRST and STT groups described the intensity of exercise as being very hard from the outset of the programme, whilst in the TST group participants described a discernable progression in intensity. (Participant interviews)	Convergent
In the PRST in most cases the participant was rating their exercise as 18 or 17 on the RPE scale in the PRST group.	Some participants perceived they could not work hard enough due to co-morbidities. (Participant interviews)	Dissonant
In the PRST group the RPE tended to fluctuate from day to day, whilst in the STT group the rated RPE did not.	Some participants had the intensity of their exercise modified to account for negative symptoms and adverse events. (Clinical record/ Physiotherapists interviews)	Complementary
In the TST component the percentage of training conducted at the specified task difficulty was 94% in the TST group. In the STT group just 37% of training was conducted at the specified task difficulty and 55% of training above.	Establishing a new RM took time. (Physiotherapists interview, Clinical record)	Convergent
In the STT group the guidelines in relation to exercise intensity were not followed.	The physiotherapist used different techniques to illustrate the concept of RM to different participants. (Physiotherapists interview)	Complementary
The rating of task difficulty did not appear to correlate or coincide with the number of progressions made in the STT group.	In the STT group the physiotherapist recorded the participants RPE in the clinical record, not the participant. (Physiotherapist interview)	Dissonant

Progression

The progression of load during the strength training component was calculated based on the percentage change from the beginning of the strength training period to the end of the

programme (Session 7 to Session 36). The increase in load was similar between the groups with the PRST group increasing the load on average, by 89% and the STT group by 92%.

The progression in the task-specific training component was evaluated by counting the number of modifications made to each task and calculating the average number of modifications per session. In the STT group the average number of modifications made over the duration of the programme was 46 and the average per session was 1.3. More modifications were made in the TST group with an average total of 74 progressions made over the duration of the programme and an average per session of 2.2. This indicates that on average participants in the TST group had their training progressed more frequently than the STT group participants.

Modification

In addition to adverse events reporting (refer to Section 8.4.8) a search of clinical records was undertaken to identify negative symptoms associated with the exercise intervention which may have necessitated modification to the intervention. These symptoms are described in Table 8-21.

Table 8-21 Symptoms in Response to Exercise

Group	Description	Modifications to intervention	Related to a medical condition
PRST	Postural hypotension in standing exercises.	Rests after standing exercises.	No
PRST	Exacerbation of knee pain	Reduced exercise intensity and volume for one sessions	Yes, knee pain
STT	Postural hypotension on rising from lying exercise.	Modification of exercise to a more upright position. Rests after exercise.	No
STT	Exacerbation of OA Knee Pain with sit to stand exercise.	Reduction in intensity of exacerbating exercise for remainder of intervention.	Yes, OA knee
PRST	Groin pain with hip flexor exercise.	Reduced exercise intensity for one session. Focus on improving technique.	No
PRST	Exacerbation of hip/thigh pain with hip flexor exercise.	Focus on improving technique for two session	Yes, hip pain

Data Integration

Table 8-22 triangulates quantitative and qualitative data for intervention fidelity in relation to the progression of exercise. Triangulation indicates highlights considerable discrepancy between the data sets including quantitative data and qualitative data provided by the physiotherapist and participants.

Table 8-22 Intervention Fidelity- Progression – Data Integration

Quantitative Findings	Qualitative Findings	Triangulation
In the strength training component the percentage of change in load from the beginning to the end of the programme was similar between the PRST and STT groups.	Some participants perceived they could not progress the load of the strength training component due to co-morbidities. (Participant interviews)	Complementary
In the task-specific training component the TST group had on average a greater number of total progressions per participant than the STT group. In the STT group the guidelines in relation to exercise progression were not followed.	One older participant load could not be progressed sufficiently during the strength training component due to fatigue. (Physiotherapists interview)	Complementary
There were a number of differences in exercise progression between the STT and TST groups. The STT group did not; • utilise secondary tasks as readily, particularly physical secondary tasks • use a random practice structure in the later part of the programme	One participant load could not progressed sufficiently during the strength training component because she was uncomfortable working at high levels of effort. (Physiotherapists interview)	Complementary
• utilise other exercise environments (i.e. the corridor and outside) • utilise variability in training as readily as the TST group	Two participants commented negatively on the repetitive nature of the training programmes. (Participants Interviews)	Dissonant

Acceptability-Participants

The rationale for selecting a qualitative approach to intervention acceptability is discussed in Chapter 8 and the aims and methods for this aspect of research are outlined in Sections 8.4.4 and 8.4.9. Thirteen of the fourteen participants interviewed across the three intervention groups expressed strongly positive views about the interventions. One participant, who discontinued PRST intervention at Week 5, expressed negative views.

The interventions were deemed acceptable by the majority of the participants. The relative acceptability or perceived value of the interventions appeared to be mediated by a number of broad and inter-related factors. These factors were found across the intervention groups; there were very few intervention or group specific differences in the findings. Where there were group or intervention specific findings these are described in

the text. Each theme and the respective sub-categories are outlined below and described in the text below.

1. *Making progress*
   - Experiencing success
   - Identifying gains
   - Becoming confident
   - Seeing possibilities for the future
2. *Sourcing motivation*
   - Self-motivation
   - Other sources of motivation
3. *Working hard*
   - Physical and mental effort
   - No pain-no gain
   - Slogging it out
4. *The people*
   - The group
   - The physiotherapists
5. *Fit with me*
   - Being older
   - Stroke effects
   - Meeting my needs
   - My kind of exercise
6. *Fit with my life*
   - My schedule
   - Routine
   - Life's challenges
   - What makes it easier

Making Progress

The experience of success during the intervention and the identification of positive outcomes in response to the intervention appeared to be a powerful modifier of participants' perceptions of the intervention. Participants who more readily identified gains in response to the intervention tended to have a more strongly positive view of the intervention. However, this sense of making progress was not just related to physical function, nor specifically related to the primary outcome measure of walking speed, but included experience of success with individual exercises, improvements in impairment, activity level and participation, gains in confidence, changes in personal relationships and the capacity to make plans for the future.

Experiencing Success

The ability to achieve and progress in aspects of the intervention itself was an important marker of success for many participants, with nine participants describing specific gains they made during the intervention.

I know I was getting to the stage where I could push and lift more – that was good. (Sonia, Age 73, PRST Group)

I couldn't go down on my knees and by the end I could actually go down on my knees, sit down on my bottom, stretch my legs and do the reverse and get up again, you know, which is a big thing for me. (Tania, Age 51, TST Group)

Identifying Gains

Participants identified a range of gains in impairments including; cardiovascular fitness, endurance, strength, range of motion, muscle tone, and mental alertness. All participants described gains in their locomotor abilities, although the scope and magnitude of the change varied among participants. Thirteen participants described gains in aspects of walking including speed, endurance, risk of tripping, aesthetics, dual tasking, use of aids, and the ability to move in different directions and over different terrains. Participants also described locomotor ability gains in stair climbing (n=4), standing balance (n=3), sit to stand (n=1) and getting up and down from the floor (n=1). Three participants, all of whom were dysphasic, described gains in their communication ability.

Before I started the programme when I walked, I would limp. And now I don't, I just walk. (Carolyn, Age 50, STT Group)

And walking stick I've changed it from the big square one, the steel one I used to have, to this light one…And also getting out of the chair is a lot easier, than taking about 20 minutes to try and get up. (Jonathon, Age 56, PRST Group)

Eight participants described gains at a participatory level. Participation gains included taking on roles within and beyond the home, and engaging in sporting, leisure and social activities.

I actually, before the programme I didn't want to go to shopping centres – I was too scared people would bump into me and the thought of an escalator just frightened the daylights out of me. I didn't know how I was going to manage and I didn't like the idea of going to shopping centre and having to ask for a wheelchair and then go through that whole rigmarole. But, you know, I needn't have feared because I walk in the shopping centre and I've gone up and down escalators. (Tania, Age 51, TST Group)

Gains in activity and participation also appeared to have an effect on the participants' personal relationships. For example one participant described how her young niece had her first sleepover at the participants' house,

> *Whereas before, no she didn't really stay with us because they (the participants sister and brother-in-law) knew that, you know, for, you know, like not that I couldn't do it possibly but it would be difficult for me to do and, and to get up and down the stairs, you know, she's running up and down like the wind, you know. And for me to follow her, well see now it's no problem, I can get up and down those stairs just as almost as fast as she can now. So it really has made a difference. (Lee-Ann, Age 68, STT Group)*

Whilst another participant described how gains in her endurance had influenced her ability to socialise with her friends;

> *I used to have to say to people after half an hour, oh gosh, you know, I really need to go and lie down now because this is all too much. But now I can actually now sit and do a full visit, a proper visit, you know. And with many people talking around me and I just so you know it feels so much more back normal. (Tania, Age 51, TST Group)*

Becoming Confident

Participants also reported gains in confidence; seven participants talked about increasing their confidence in relation to balance and walking.

> *Well I think it's given me a bit more confidence because I'd lost it....I think it's given me back a bit more confidence than I did before because at one time I was sort of jittery going anywhere, you know ...this has given me a bit more confidence and I'm doing things now I didn't think I could do. (May, Age 90, STT Group)*

Seeing Possibilities for the Future

For some participants the intervention appeared to highlight potential capacity and future possibilities which enabled them to make plans for the future.

> *Yeah, I feel more confident using the walking stick and I'm looking forward to the time when I can dispense with the walking stick. (Brian, Age 73, TST Group)*

> *It's very nice to be able to just move outside of that space of, you know, you're confined to your limitations, you're confined to your areas of comfort like your bed and the one seat that you always sit on and the people that you used to having with*

you... Before the programme I really, I was thinking that I really have to start working on myself and I accept that I am now a disabled person, you know, and I don't feel that anymore. I now just think well there's some things I can't do but, you know, if I keep trying then I will be able to do them. Let's just keep going, even if it takes five years, even if it takes 11 years. (Tania, Age 51, TST Group)

To summarise, a sense of success with the intervention, the identification of gains which extended beyond activity to gains in participation and confidence appeared strongly related to the intervention acceptability; where individuals who identified large or significant gains were more likely to describe the intervention in a highly positive manner. The positive influence of these gains was also powerful when reinforced by others including family, friends and acquaintances, other group members and the physiotherapist and therapy assistant.

Sourcing motivation

All participants referred to different sources of motivation which encouraged their initial engagement with the programme and then fostered their continued participation.

Self-motivation

A strong theme which was identified by ten of the fourteen participants was the importance of self-motivation. Self-motivation and determination were discussed with reference to the individuals' and by those offering opinions about what was necessary for others to successfully engage.

Interviewer: And what helps you take part in it, what has helped you take part in it?

I think it's my self-determination...

Interviewer: And what do you think has helped you achieve those goals?

Hard work. And a hundred percent commitment from me. (Carolyn, Age 50, STT Group)

Key thing is, you know, getting your mind stuck to what you're doing to improve your health and turning up when you're needed, you know, on the day...The things got harder like there's a couple there that couldn't take it but I wasn't going to let that, you know, stop me because I had a goal and you don't give up half way. You've got to go all the way if you know where you, what the outcome is. You won't find the outcome until you do the whole lot, you know (Jonathon, Age 56, PRST Group)

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Other Sources of Motivation

The participants also described external sources of motivation including family, having an altruistic view of the research process, other members of the group. The power of the group as a source of motivation and the role of the physiotherapist as motivators are discussed in greater depth in the section The People. However, whilst external motivational factors appeared to be important in relation to the acceptability of the intervention, on balance, self-motivation appeared to be a much more powerful moderator. Those who described high levels of self-motivation and self-determination were more likely to view the intervention positively.

Working Hard

Physical and Mental Effort

Thirteen of the fourteen participants described the intensity of the interventions as hard,

> *Yeah, I put, I mean the pushing the various weights and things, that was so hard. I was sweating straight away, you know, that was, you put maximum effort in once you got, particularly when we got to the point where we had to do things fast. (Jeff, Age 70, PRST Group)*

Participants frequently described the level of physical and cognitive effort required to complete the intervention, and reported fatigue in response to the programme. The level of effort and consequent fatigue was often referenced to changes in intensity of the intervention as the programme progressed.

> *I thought the intensity was really good because it made you focus. (Lee-Ann, Age 68, STT Group)*

> *I could just give it everything I've got, you know and then I go home and I'd be so exhausted (laughing)…And sometimes even towards the end I would be still tired the next day but I'm ready to get it all over again following day. (Tania, Age 51, TST Group)*

The level of effort required and fatigue were accepted as normal responses to high intensity exercise by the participants and did not appear to negatively influence the acceptability of the intervention. As discussed in the section Making Progress a reduction in fatigue was often viewed as markers of success, as the symptoms reduced over time, which participants equated with improvements in their fitness and endurance.

No Pain-No Gain

Two participants in the PRST group, four in the STT group and all participants in the TST group linked how hard they worked during the intervention to the gains they made and their sense of achievement.

> *I mean, no pain no gain isn't it, you know, so um no well what I put in no, it was benefiting me, you know. Like, I mean, the more I put in, the more benefits I was getting out of it. You can cheat or you can do it properly so I opted for the, you know, the latter, do it properly. (Jonathon, Age 56, PRST Group)*

> *I think the, what I really enjoyed the most was that starting off I didn't think I was going to be able to do it but I just thought, oh well, you know, they think I can so I must be able to do some of this. And I started in I just got harder and harder as the time went on but actually I started being, feeling that I wanted it to be harder, you know. And I wanted to continue to be a challenge and they responded so well to that, you know, they really did challenge me and I loved it. Honestly I did yeah. I was excited about coming and then when I was here just so, it felt like I, I could just give it everything I've got, you know and then I go home and I'd be so exhausted (laughing). (Tania, Age 51, TST Group)*

Participants appeared to directly relate the intensity of their effort and work with the gains that they made. Participants also spoke about specific exercises which they found challenging. This challenge often came with a sense of frustration when the participant perceived they had not achieved the exercise. Once an exercise was mastered participants described a strong sense of success (as discussed in Making Progress). However any sense of frustration with individual exercises did not seem to unduly influence the acceptability of the intervention as a whole.

> *No, my least favourite exercise was the rubber bands moving it sideways…Oh that was difficult too. Um couldn't stretch as far as I wanted to with it. Actually that one annoyed me. I mean, I don't think it should be taken out or anything like that and you did it each week. You can't like them all. (Jeff, Age 70, PRST Group)*

Slogging it Out

Four participants commented on the repetitive nature of the training programmes. Two participants spoke negatively about this, citing a lack of variety in the training, particularly

in the later weeks of the programme. One of these participants was from the STT group and one from the TST group.

> *I don't think there's anything that I really didn't like but I did get a little bit bored with the exercises, especially in that last block, even though it made me very tired at that next level once I was working at that very hard level I didn't know how to challenge myself anymore. (Tania, Age 51, TST Group)*

> *Maybe they could set us or people with different machines. As well as what we did. Still do what we did but have more variety…It would um make it a little, a little less of a pain in the arse for us. (Carolyn, Age 50, STT Group)*

In contrast, two participants, one from the STT group and one from the TST group, spoke about the repetitive nature of the training as a positive factor.

> *And also like the it was repetitive but a repetition might normally be a bit boring but it wasn't. You could feel yourself getting better as you, as you repeated the exercises. (Brian, Age 73, TST Group)*

The requirement to work at a high intensity during the intervention did not appear to negatively influence the acceptability of the intervention. In fact, many participants valued how the intensity of effort forced them to focus and work hard, and they closely linked this to their sense of success with the programme.

The People

The role of people involved in the intervention, including the other participants and the staff, is closely linked to the section Sourcing motivation. Whilst this section further highlights how other participants and the staff acted as external sources of motivation for many participants, it also describes broader concepts of caring, belonging and camaraderie which are not encapsulated under the concept of motivation.

The Group

Twelve of the 14 participants referred to the group positively, describing a sense of belonging, camaraderie and caring.

> *I feel it was almost like a family in the end, you know, with 12 weeks of five people, although we didn't have time to talk, you got to know them and it was a really nice feel…Perhaps if you were there on your own it would be clinical, for want of a better expression. You're on your own and you've got to do this, but the others in a group it*

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was a nice feel, kind of friendly and encouraging and interesting to see them and how they were doing. (Sonia, Age 81, TST Group)

I looked forward to coming to the sessions each time and it gave me a feeling of belonging, that's what it amounted to…Oh I felt, I felt that somebody, this course, that somebody cared. That was the other thing, you know, that I belonged to a group of people and tutors that cared. (Mark, Age 81, STT Group)

Participants also felt a strong sense of obligation to the group; their individual level of effort was reflective of the group and they could not be seen to be letting the team down.

…I feel if I didn't I would let down the team. (Carolyn, Age 50, STT Group)

The group provided an external source of motivation for many, with some participants describing an active process of supporting one another to work hard.

Well actually it was quite good in a group because we all helped each other, we all looked after each other –you can do it, you can do it". (Jonathon, Age 56, PRST Group)

The diversity of the groups' make-up was cited by five participants positively, and in some cases, with surprise at how well the group interacted and supported one another.

Oh no it's um good mix… Yeah it's been good yeah. Mixtures of women and men. They all get on. I'm surprised at that. (Jeffrey, Age 63, STT Group)

Reference was made to the influence of specific members of the group and their capacity to inspire others. In particular, participants talked about those members of the group who were older, more severely affected, those who had made good recovery and those who were longer since stroke as providing a special source of inspiration, primarily because of their capacity to continue to work hard and make gains.

…what was encouraging also is the people in the group, the way the group was put together. They were inspiring to me too, you know, somebody who's, you know, maybe 20 years older than me and doing everything that I have to do and, you know, and going for it… So in that first week I had to give myself a good talking to and say, 'Listen, those people are much older than you and you're sitting there complaining – now get on with it'. (Tania, Age 51, TST Group)

The group also provided a sense of competition for some participants, with six participants making reference to competing with other members of their group during classes. Whilst this was more overt in the PRST and STT groups, where participants

actively compared the load they were managing, it was also evident in the TST group, where participants compared task difficulty and intensity of effort.

> *Yeah and also I think seeing other people you think, "Mm if people can do that, well I can do that", or "Don't want you to do better than me". (Sonia, Age 81, TST Group)*

However, for one participant in the PRST group, the competition between other members of the group and himself was viewed negatively.

> *It was only that I got worried at the finish that I wasn't going to keep up with the others in what weights they were shifting.*
>
> *Interviewer: Okay, so did you feel like you were competing with the other people doing the programme?*
>
> *In the early stages yes. And I did right up to we shifted to eight movements per machine and that's where I broke off. The other two were males, were using bigger weights than me at the finish … but I handled what I could. (Thomas, Age 92, PRST Group)*

The Physiotherapists

Twelve of the 14 participants interviewed discussed the role of the physiotherapists and therapy assistants in their positive views of the intervention. Participants valued the therapists' clinical expertise, the care and attention they provided, their ability to motivate and help the participants to maintain focus during the training and their belief in the participants' capacity to be successful.

> *And I think what was amazing for me is that physios can, they don't look at you and see your limitations, they see actually what you can do. And you can't see it yourself and then they create a situation in which you can try those things that they can see that you will be able to do one day, you know, and they really tap your potential and just nudge you on and on bit by bit. You know, they um I think they helped to, in each person, to find just that next bit of strength. To just try again and try more…, in the time you really try, I'm really getting my, leaving my life in their hands, you know. And I felt, I felt so much trust and confidence in the ability and how they came across with what they say and how they did the instructions and the support so and that's also important. (Tania, Age 51, TST Group)*

They weren't bullies. That's the first thing but they had a way of getting you to do things without stand over methods. Yeah they pushed me and but being firm and if I try to be super silly or anything like that they soon caught on to it, you know, and just brought me back to earth...That was the other thing, which is interesting, was that they didn't, they were very attentive people. They observed when you had finished a machine so there was no sort of having a little daydream because they were on to you. (Mark, Age 81, STT Group)

The people involved, including the other participants and the physiotherapy staff seemed to be a powerful influence to enhance the acceptability of the programme. This influence extended beyond motivation, and included aspects of group obligation, inspiration, competition, care and camaraderie.

Fit with Me

All of the participants discussed the suitability of the intervention for themselves and for others. Participants described how well the interventions met their needs and goals, factors about themselves and others which might impact the effectiveness of the intervention or a person's ability to engage with it. A number of participants described the intervention as being suitable for everyone, some referring not only to people with stroke or those with walking disability, but to otherwise healthy individuals.

Being Older

Two participants in their nineties spoke about the effect of their age on the suitability of the programme for them; age was apparent moderator of acceptability and the expectation of a highly positive outcome.

Well fitness is hard thing to answer because I'm now 93. So I've got to expect deterioration in my body ...I think the fact that I'm still getting about at this age. It hasn't done me any harm....Nobody can foresee when they're going...No because of my age I won't plan ahead extensively. (Thomas, Age 92, PRST Group)

Stroke Effects

One participant described how she would have benefited more from the programme had she received it early after her stroke. Another participant hypothesised that the time since stroke would be an important factor for others. Severity of stroke was mentioned by one

participant as a potential factor which would limit others' engagement with the programme.

> *Well I wouldn't recommend it to anyone that, that's, you know, you know, they've done all they can and, you know, and they're bedridden and all that…*

Although, this participant went on to say,

> *Even if you were crippled or something you'd probably get that 2%, 1% difference and that's enough. (Jonathon, Age 56, PRST Group)*

In contrast, when discussing the influence of severity of stroke on the ability to participate in the intervention another participant said,

> *…each person has their strengths and the people that are doing, taking the course, seemed to know our strengths and they regulated according to our strengths so even if it's, you know, somebody who's a lot weaker, you know, they would accordingly do, you know, a low intensity for them than they would for somebody who was a lot stronger. (Lee-Ann, Age 68, STT Group)*

None of the participants who were more severely affected by their stroke identified their level of disability as a limiting factor for engagement.

Meeting My Needs

Another apparent moderator of the acceptability of the intervention was the degree to which the intervention met the individual's needs. This related to the actual content of the exercise programme and the context in which it was carried out.

Two participants perceived the unilateral nature of the PRST component as inappropriate for their individual situation.

> *I could never quite understand why you worked the one leg in my case when I had polio in this leg and the stroke I've had in this leg and I could never quite fathom why, but I wasn't going to sort of get into a long discussion with the instructors about it all. I didn't feel it was my place to, but perhaps they could have asked a little bit more and exercised both legs while I was on the machine. (Mark, Age 81, STT Group)*

The fact that the upper limb was not overtly trained as part of the intervention impacted the acceptability of the intervention for five participants. For two participants this was a significant concern,

Oh my legs getting better but my arms, you know, that's the worry. I've lost the strength in it, you know. (Jeffrey, Age 63, STT Group)

For the other three participants this did not appear to impact the acceptability of the intervention however, they had each independently made plans to utilise similar training concepts to work on regaining function in their affected upper limb.

And I'm now going to try to find the gym where I can do the same with my arm. (Jeff, Age 70, PRST Group)

Participants who had comorbidities described how this limited their participation in the programme.

I've been having back pains... And so I had to limit the people as to how much pressure they could put on me. But I survived the lot. (Thomas, Age 92, PRST Group)

Two participants described how the outpatient based nature of the intervention combined with a limited social support network meant that they were unable to translate gains made during the intervention into their home environments.

My Kind of Exercise

Some participants described their previous experience of exercise and the type of exercise they enjoyed doing; relating this to how much they enjoyed the intervention. These effects acted on the acceptability of the intervention both positively;

Well I enjoy, I always have enjoyed kind of gym and I've always been a going, you know, doing things, little girl banging a ball against a wall and always never still. So I enjoyed this activity. (Sonia, Age 81, TST Group)

And negatively;

"Well I hate the gym to start with. I'm a walker, I'm a tramper.

Interviewer: Right so are you saying that strength training is sort of not appealing to you?

Well no, never was. I did come because we thought well it's going to perhaps benefit someone else. No I hate the gym. I've been many times. But I hate it. I'm an outdoors person, I'm a tramper, abseiling, pétanque, tennis – you name it but gymnasiums no way. No, I have tried it tons of times when I've had to do it... Psychologically I don't. Well, I can't say I don't like it, I just it's just not me." (Sonia, Age 73, PRST Group)

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In summary, the acceptability of the intervention appeared to be moderated by a number of personal and stroke related factors. However a key influence of intervention acceptability seemed to be the extent to which the intervention met the individual's needs; the less relevant the individual perceived the intervention to their specific needs the less positively it appeared to be viewed.

Fit with My Life

The ease with which the commitment to exercise three times a week for an hour was integrated into their lives was discussed by 11 of the 14 participants interviewed. Participants also discussed factors which helped or hindered their participation and the effect of unexpected and expected life events on participation.

My Schedule

For some participants, the exercise programme represented a challenge to accommodate in their weekly schedule. However, the relative disruption appeared to be strongly influenced by how important they perceived the intervention to be to them, and how much value they placed on it.

> *You're never going to find the exact perfect time. It wasn't convenient for me; it was 11 to 1, 11 to 12 or 11.30 to 12.30 I think, yeah. That wasn't convenient for my work because I'd go to work and then I'd have to come here... just how they affected me personally, I do it, I adjust my personal life to live around it. (Jeff, Age 70, PRST Group)*

> *There were two reasons, one was the interruption of my routine where my time and the fact of not having any choice of what time I would come. (Sonia, Age 73, PRST Group)*

Routine

The routine and commitment was also described in a positive light, as a method of prioritising exercise and rehabilitation, which might not otherwise happen if they were exercising independently or in their own homes. The intervention also provided a sense of structure and purpose to some participants' days, which was also highly valued;

> *I just think just having to be here, you know... Oh the discipline of just coming here, you know...Yeah, structured yeah, yeah. Yeah it's been good for me. (Jeffrey, Age 63, STT Group)*

Life's Challenges

The influence of unexpected life challenges on the ability to engage with the intervention and the consequent acceptability appeared to vary among participants. For example, one participant who had a hospital admission for an unrelated medical problem was very challenged by the effect of that life stressor and the disruptions it caused to his life. The burden of this event alongside the commitments of the intervention appeared to be overwhelming for this participant. In contrast, another participant who experienced exacerbations of his osteoarthritis in response to the intervention and had to seek medical advice was less challenged by these events. This was echoed by two participants experienced injuries in response to the intervention, which are discussed in Safety. For one participant, this was not an issue and she did not discuss this minor injury during her interview. However, for the other participant, the injury she sustained was a significant contributor to the unacceptability of the intervention for her.

> *...I was lifting 8 kgs. And it was easy and I was going too fast. And I guess that's what caused it...I came back a day later, I don't know, I came back twice but it was still too painful. I didn't come back. I wasn't going to take that risk again. Because it was quite a bad injury from my knee and it went right up into my back. Well I wasn't going to put myself in that situation again. (Sonia, Age 73, PRST Group)*

What Makes it Easier

Participants identified other factors which had facilitated their participation in the intervention. These included the provision of transportation, the location of the venue, accessibility of parking, the availability of amenities such as the onsite café, administration and reception support and family support.

In summary, the majority of the participants rated the acceptability of the interventions very highly. No between groups differences in acceptability were identified. Relative acceptability appeared to be influenced by a number of inter-related factors. Making good gains in response to the intervention acted as a strong positive moderator of intervention acceptability, particularly when those gains extended beyond activity to participation, confidence and seeing possibilities for the future. Sourcing motivation was also seemed to be an important factor, with self-motivation being a key element. The group and the physiotherapist proved strong positive moderators of the intervention acceptability, acting not only as motivators but also as supportive social network. Intervention

acceptability was challenged by the extent which the intervention design met the needs of the individual and fit with their lifestyle.

Acceptability-Physiotherapists

The question of intervention acceptability from the perspective of the physiotherapist was addressed via qualitative analysis of the physiotherapist post-intervention interviews and the weekly feedback summaries completed by the physiotherapists throughout the intervention phase.

The rationale for selecting a qualitative approach to intervention acceptability is discussed in Chapter 8 and the aims and methods for this aspect of research are outlined in Sections 8.4.6 and 8.4.9. In brief, a qualitative descriptive approach was used to allow the physiotherapists an opportunity to express their thoughts about the acceptability of the intervention and to offer suggestions for the refinement of the intervention.

All three physiotherapists expressed positive views about their respective intervention. The highest level of acceptability was reported by the TST and STT physiotherapists, whereas the PRST group physiotherapist, whilst positive, was more circumspect in her discussions. The physiotherapists' relative acceptability of the interventions appeared to be mediated by a number of inter-related factors. These factors were found across the intervention groups; however, different factors had a greater or lesser role in intervention acceptability for different physiotherapists. These differences are highlighted in the text below with reference to aspects of the intervention component or group, where relevant. The findings are illustrates by five themes which influenced intervention acceptability.

1. *Seeing participants improve*
2. *The details*
   - Learning the ropes
   - Being busy
   - Circuit timing
   - Documentation
3. *A new way of working*
   - Intensity versus Quality
   - Getting the intensity right
   - Highlighting capacity
4. *Working with a group*
   - The individual vs. The group
   - Managing social interactions
5. *New Understandings*
   - Underestimating people with stroke
   - Changing my practice

Seeing Participants Improve

The physiotherapists described at length the gains which the participants in their groups achieved during the intervention. They primarily reported gains in activity, although there was some focus on gains in impairment, participation and confidence. The TST and STT physiotherapists described a greater breadth of gains compared to the PRST physiotherapist.

> *Confidence in her balance and being able to walk....you know, that changed around quite a bit towards the end after the study and she booked her holiday, was looking forward to going and she said she would never would have been able to go prior to the study. (Belinda, Physio, STT Group)*

The extent to which the physiotherapist readily identified gains in their participants appeared to relate to the extent to which they found the intervention acceptable.

The Details

Many of the physiotherapists' reflections of intervention acceptability focused on the practicalities of implementing their respective intervention with their group. Overall, the physiotherapists were strongly positive about the ease with which their intervention could be implemented based on their training, the intervention manual and the communication and support systems imbedded in the intervention design.

> *And she told us, well she told us everything and we got it in writing... So I think the training was sufficient because it is actually doing it that brings up the questions and the things. But I felt like I was well prepared for everything, I knew in every situation what I was supposed to do and not. (Angela, Physio, TST Group)*

However, four sub-categories were identified which potentially influenced intervention acceptability including: learning the ropes, being busy, circuit timing and documentation.

Learning the Ropes

Initially it took some time for the physiotherapists to learn the specifics of the intervention and to become familiar with the needs of each of the participants. Whilst there was a two week familiarisation period built into the programme, this phase of the intervention appeared to be more comfortable for some physiotherapists than others. The TST and STT physiotherapists both appeared at ease with the degree of learning and uncertainty;

It might have been initially everyone looked a little bit chaotic but we had it under control and then after maybe one or two changes everyone sort of got into the same rhythm. (Belinda, Physio, STT Group)

In contrast, for the PRST physiotherapist the process was less comfortable;

I think that in the first week or two could have either had more, more support. I think the first couple of sessions I did have another person to come in to help. The first couple of weeks when people were learning to use the equipment it was quite challenging … Or I thought, I think I thought that it was challenging at the time but really once I guess the first couple of weeks were always introduction time anyway… By the end of the programme we could be moving around the room and as soon as you saw someone at a particular station you knew exactly what they needed in terms of assistance setup and what weights needed to be there and what adaptations they needed. Whereas I guess in the first few weeks that was what you were all learning. (Michelle, Physio, PRST Group)

Being Busy

All of the physiotherapists described being very busy during the class. This assiduity related to many factors including managing the needs of five people, the needs of more severely affected participants, the intensity of the programme, the need to manage equipment and transitions of participants between stations and the social interactions of the group.

Yeah for being able to get around to five of them and even then, you know, it was quite stretched at times …because it was a smaller group of five participants, although at times it was hectic, well not hectic but busy for the physio to get around to those doing the different exercises. (Belinda, Physio, STT Group)

This busyness seemed somewhat overwhelming for the PRST physiotherapist, whilst in contrast the STT and TST physiotherapist valued this sense of busyness.

It was really exciting going in there, I was never ever bored. I couldn't believe how fast the time passed, that hour was nothing and then walking round the different people, all the different characters. It was so much fun, it was fun watching them, you know, starting greeting each other with names and asking how they were and yeah, you know, things like that. It was great. Like I could have done another three months without any problems at all. (Angela, Physio, TST Group)

Circuit Timing

There were differences in the ability to maintain the timing of exercise to transition/rest among the groups. In the PRST and STT groups, as the number of repetitions per set decreased in the PRST component, the duration of time ascribed to each set became less suitable.

> *We did notice as the study went on and they were doing less reps, the timing was out quite a bit for the two minutes for the strength exercises ... it was taking them a lot less time to complete their exercise with doing only eight reps. (Belinda, Physio, STT Group)*

In the STT group, this meant that participants were encouraged to transfer to the motor skill component as soon as they had completed the set. Whilst in the PRST group, the participants completed progressively more rounds of the programme and by the end of the programme they were completing three sets of each exercise within a 40 minute timeframe.

> *And so it had started out as an hour programme and people were completing the full hour's exercise... and so they ended up kind of doing more like a 40, probably 30 or 40 minute programme for some people. (Michelle, Physio, PRST Group)*

Consequently, the timer system was less successful for these two groups. In the TST group the timing worked well throughout the programme.

Documentation

The documentation system involved each participant having their own exercise programme printed for each session and attached to a clip board, and the participant recording the intensity ratings for each exercise and amending the form to reflect any changes from the planned programme. This was a challenge to manage during the intervention session. The physiotherapists reported difficulties with participants being able to physically manage the clipboard and also in cognitively being able to interpret the exercise programme documentation.

> *I think perceptually he really struggled with completing the form (Michelle, Physio, PRST Group)*

> *...Because there was just five separate bits of paper so trying to record on five different things – that in itself was, you know, a little bit challenging... Rather than*

have, because we had to keep going back to, back to where we kept the charts rather
than carrying them around because it was just too cumbersome and you were having
to adjust weights and having to go back to write things down was just another factor.
(Belinda, Physio, STT Group)

However the requirements for the physiotherapist to update the programme and plan for
the following session using an Excel® spreadsheet was well received,

A New Way of Working

All of the physiotherapists described how the intervention challenged them to work in
new ways. These new ways of working appeared to bring tensions to the physiotherapists'
perception of the intervention and were often viewed as both positive and negative by the
same therapist.

Intensity versus Quality

One of the most striking differences the physiotherapists described as a deviation from
their normal physiotherapy practice was the requirements of the intervention to progress
exercises based on intensity rather than on the quality of the participants' movement.
Exercises were progressed based on perceived difficulty (TST component) or repetition
maximum (PRST component). Given the group structure, the intensity of training, the low
rest ratio and continual progression of exercises the physiotherapists had limited time to
address quality of movement with their participants. They were restricted to providing
instructions to the participant to focus on movement parameters or outcomes of
importance, or in the TST component to set up the task in such a way as to focus on
specific aspects of the movement, or in the PRST group to modify or support the
participants position using equipment such as straps. This left very little scope to provide
hands on facilitation of movement. All the physiotherapists spoke about this and described
how this emphasis toward intensity of training and away from quality of movement
challenged them on a professional level.

It was a huge challenge... Do we just make people work hard? or do we actually
provide them with individual physio? Because there's loads of people I would have
wanted to actually give them a physio session and work on pure quality rather than
just working on the exercises. And we were told that it was basically you can correct
them and tell them what they're doing wrong but you shouldn't constantly stay on
the side and say nicely, nicely, nicely. So we did a mix. (Angela, Physio, TST Group)

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I think one other thing we had to be careful was that with people being really keen to increase their weight load that was the thing that I found was everyone wanted to increase, they wanted to increase their weight but didn't necessarily notice if by increasing the weights they throw your technique right off or that they were only completing an exercise through part of their range of movement. (Michelle, Physio, PRST Group)

As a physio, I didn't feel at times I had the time to be able to spend on one participant to sort of maybe alter a bad habit or, you know, correct a pattern of movement that, you know, you could help them more with. I mean, there was some that you could, but then you'd have to change and so it was just the nature of the programme. (Belinda, Physio, STT Group)

The physiotherapists also described the need to re-focus the participants' attention on quality of movement each time the intensity of the training increased, particularly in relation to the PRST component. However, the focus on intensity of training rather than quality of movement was very liberating for one physiotherapist.

The other thing I liked, which I've never done before, because we usually look at quality of movement and getting things better, is working to a certain level of exertion. Like I'd never done it before…I thought it was, that was really interesting to watch that or to work under that sort of hat rather than under the hat of prove your quality or your repetitions, you know, your weights or something. That was interesting so I thought they all found it beneficial. I loved it, I loved doing it. (Angela, Physio, TST Group)

Getting the Intensity Right

All of the physiotherapists described working hard to progress and modify the participant's exercises to achieve the desired intensity of training. However, this did not seem to be viewed negatively, rather the need to modify and progress was considered one of the advantages of the interventions.

The other thing that was really good for me is the being, you know, getting inventive with having one exercise and changing it, not making it harder but just using different ideas and different things to do the same exercise in a slightly different way. (Angela, Physio, TST Group)

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Oh I think that um the changes in the programme as we increased the intensity and lowered the repetitions it was always good to have a change in the programme. (Michelle, Physio, PRST Group)

Modifications were not only required to accommodate progressions within the programme, but also to accommodate variation in a participant's ability on a given day and even within a session as the person fatigued.

But there was one businessman who also had, you know, quite bit of knee pain so his weights sometimes; we had to alter from day to day. … if they hadn't had a very good sleep… so there were other factors that also contributed to how hard they could push themselves on a particular day. And then there was also illness, colds and things …You couldn't make the assumption that because they did it last time that they'd actually be able to do it this time (Belinda, Physio, STT Group)

Achieving the desired intensity of training appeared more challenging in the PRST component. The physiotherapists described developing different strategies for different participants to ensure that they were working at the correct repetition maximum.

It would be like, "Oh no that's too heavy, that's too heavy, I can't do it". But then, you know, sometimes you'd take like the minutest amount of weight off and they'd do the next one and I'd put it back on again and they'd be able to do the reps required. And sometimes if you took it off they'd do more than the set rep you wanted …so that was quite tricky as well was just working out the appropriate target weight for them for the required RM. And then it was just also talking to them saying, you know, "Oh that's too light" (laughing). I'd say, "How many did you do?" They're like, "Oh ten" or something. "Oh well we need more weight then." "What!!" (laughter). "You're doing too many." So and then after a while they got into their own pattern with it. (Belinda, Physio, STT Group)

In most cases, the physiotherapist was aiming to increase the intensity of the participants' training but for a few participants they were aiming to reduce the intensity to ensure that they exercised in a safe manner and were able to continue for the whole hour.

In summary, the physiotherapists' interviews and weekly feedback forms highlighted how the interventions challenged them to work in new ways. In particular, the requirement to focus on the intensity of training rather than the quality of movement as the primary parameter for progression was challenging. In addition physiotherapists were less familiar

with establishing intensity for PRST training using RM and consequently spoke of devising new ways of working to achieve this with their participants.

Working with a Group

At a broad level, the physiotherapists described enjoyment at being involved with a group of people for a period of time and observing the efforts and gains the participants made.

> *I found it really good, I really enjoyed being involved and actually taking the classes. You know, it was quite good to,I think the group environment with the participants was quite enjoyable, you know, they had fun, which you know, I quite liked as well as seeing the effort that they were putting in some of the, you know, gains that they were getting from all the effort as well was quite rewarding. (Belinda, Physio, STT Group)*

The Individual versus the Group

One of the challenges identified by all the physiotherapists was the need to balance the requirements of individual participants against the needs of the group. Often, this related to individuals with more severe strokes, who were more physically dependent,

> *A mixed ability class is challenging. High functioning participants are not receiving the guidance to progress loads as much as required while a low functioning participant is requiring significant one-on-one therapist/participant hands on assistance. (Michelle, Physio, PRST Group)*

Whilst the division was not strictly 1:1 supervision with the more dependent participants, this did pose a challenge for all the physiotherapists as every group had at least one participant who was more severely affected by their stroke.

> *It wasn't, I guess she had someone (the therapy assistant) with her exercising all the time but it wasn't quite the same as having a one on one physio session because the assistant could be available for someone, you know, while she was having a little bit of a rest between exercises. (Michelle, Physio, PRST Group)*

The physical dependency of the participants also made a difference to how quickly and how much assistance participants required when moving from station to station. At times, more severely affected participants slowed the progression of other participants through the stations. The physiotherapists addressed this by managing the order of the participants and using empty stations to create breathing room, as there were seven

stations and five participants. However, the physiotherapists were at pains to point out that addressing the needs of the more dependent participants was manageable, and not a reason for excluding participants from the programme.

> *I would hate to see a programme be run and to exclude people that were quite dependent and would really benefit purely because they needed a bit more assistance. (Michelle, Physio, PRST Group)*

> *…in my group I had anyone from very mild or very moderate deficits to really quite severe deficits. Physically there were no limitations whatsoever, they could all do it. Some needed more help than others but they could all participate. (Angela, Physio, TST Group)*

The issue of supervision of more dependent participants was exacerbated by the environmental requirements in the STT and TST groups. These groups used the gym, corridor and outdoor garden area for task-specific training.

> *One participant requires stand-by supervision; with participants exercising in 3 areas (gym, corridor, outside), one area will have no supervisor; this will be one of the indoors areas - one supervisor has to be outside, as some clients are unable to negotiate stairs without rails, but should be challenged to do exercises outdoors. (Angela, Physio, TST Group)*

The PRST group highlighted that the need for supervision did not relate purely to the physical dependency of the participants. Often, it was the need for support to manage the cognitive and perceptual requirements of the programme which meant that participants required closer supervision.

> *…she was particularly difficult right from the very start and the group exercise environment was particularly challenging because she really wanted one on one and it was quite difficult to disengage from her questions because I couldn't be with her for the duration of the session, so that was challenging. (Michelle, Physio, PRST Group)*

> *We found that if he was left to work through the programme on his own he wasn't changing the weights from the previous participant so often that meant that he would start off at a much higher weight and really to sort of complete it at his level he needed to have someone doing that for him. Reminders didn't really seem to be enough. It was quite constant. (Michelle, Physio, PRST Group)*

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Managing Social Interactions

The physiotherapists all described to some degree, the need to contribute to and manage the social aspects of the group. They were generally very positive about the way the groups interacted to support and motivate one another and the sense of healthy competition and group obligation which developed to facilitate the participants to work hard at each training session.

> *That was a huge part of, you know, one doing the sit to stand and just stopping half way through the exercise ...they would say, "Oh come on, get on with it – you've only got 30 seconds left" sort of thing. So they were really pushing each other and that was amazing. And I think also maybe the pressure of, "Oh, I don't want them to see that I'm exhausted", they kept on working. Then they started, well the group dynamics started quite early, the greeting each other in the morning and, "How have you been?" (Angela, Physio, TST Group)*

Each of the physiotherapists noted that there was little scope for social chitchat during the class time; socialising was limited to immediately before and after the classes.

> *There was not much talk anymore for a few sessions because they were working so hard. (Angela, Physio, TST Group)*

> *Always beforehand and afterwards they'd spend, you know, a couple of minutes talking to each other so they had a good group dynamic and they were, you know, all looking out for each other. (Belinda, Physio, STT Group)*

When participants talked during the training time, the physiotherapists described the need to help monitor and encourage a return of focus to the exercises.

> *I think it was personalities as well one would love to talk, you know, loved to talk a lot and so, which was fine but then while talking would stop doing the exercise and so it was like, you know, just monitoring that a little bit and – you can talk but you've just got to move as well (laughing). (Belinda, Physio, STT Group)*

The physiotherapists informally supported the group dynamics by helping their groups to organise social gatherings outside class times. There were celebrations of significant birthdays and a celebration of the halfway mark and end of the programme.

> *I think they found that it was nice to have something to look forward to and particularly, you know, at the end of the first few weeks or yeah I guess it's nice to have something to celebrate yeah so that um that did encourage them to stay... Yeah*

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so it was just us at the end of the group um but they seemed to really enjoy it. (Michelle, Physio, PRST Group)

But they did, yeah, they did like to have that time and I did notice on the days that we did have the morning tea together that was nice for them to have a bit of time together just talking without exercising. (Belinda, Physio, STT Group)

In contrast to the other groups, the PRST group physiotherapist described three situations in which the interactions between group members became problematic and affected both individuals and the group as a whole. For example, in one situation the participant became very upset with the seating arrangements in the shared taxi and consequently there was tension within the group.

He was a complex character, he was. Something that came up was he didn't really say very much and then all of a sudden one day he was really quite upset about the transport arrangements and we tried to deal with it and he did, did continue coming back so I guess we did, did reasonably adequately. But it's yeah, it seemed that if something upset him a little bit yeah he almost became a slightly different person in a way, yeah, which is a little bit challenging. (Michelle, Physio, PRST Group)

These situations needed careful management from the physiotherapist and this requirement appeared to influence the acceptability of the intervention for this physiotherapist. In the PRST group the need to support more dependent participants also appeared to create friction between the group members at times and this required careful management of social interactions as discussed in *The Individual versus the Group*.

I think there might have been one particular participant who found that quite frustrating that maybe he wasn't having, he was I guess quite high level had a high level abilities and was kind of getting the programme and knew what he needed but maybe wasn't getting the little bit of assistance when he needed it because time was being taken up disproportionally with others. (Michelle, Physio, PRST Group)

New Understandings

Underestimating People with Stroke

Each of the physiotherapists described how participating in the intervention had challenged their beliefs about the capacities of people with stroke. They each described how they had previously underestimated how hard people with stroke could work during rehabilitation.

They didn't have any rests and being able to push someone that far was quite an eye opener for me as well for that length of time because obviously, you know you can push a person in an exercise but to get the gains but then doing it for a prolonged period over an hour with different exercises was quite amazing to see that they could do that. (Belinda, Physio, STT Group)

For me it's yeah well first it was great to see that people could work for a whole hour and they did. I mean, they just a circuit with two minutes and 30 seconds, rest for 30 seconds. That for most people was just enough to actually walk from one station to the other, especially when we had the outside things going as well. So that basically wasn't a rest and it was just a method of working harder and resting less and they all pulled through the hour, even the people that we thought, oh he's quite old, he might not be doing it. It was really amazed how hard they could work and I think I completely underestimated that for all my physio career... (Angela, Physio, TST Group)

Changing my Practice

The physiotherapists in turn described how they would change, or had changed their physiotherapy practice, in response to this new understanding.

I think it had an affect pretty much straight away. .... I think that it's had a huge effect on my work (Angela, Physio, TST Group)

In summary, the physiotherapists post-intervention interviews indicate that each of the interventions were acceptable. Factors which appeared to moderate intervention acceptability were generally seen across the groups and related to the pragmatics of delivering the respective intervention, the challenge of training participants with a focus on intensity and the complexities of managing group interactions.

Safety

Safety of the intervention was monitored using adverse events. An adverse event was described as an event which caused the participant to seek attention from a health professional, or limited their activities of daily living for at least two days. Table 8-23 Adverse Events describes the adverse events reported in the trial.

Table 8-23 Adverse Events

Group	Description	Severity	Medical Intervention	Modifications to Intervention	Outcome	Related to trial	Related medical condition	Method identified
STT	Fall at home.	Minor	GP Review	Reduced exercise intensity and volume for two sessions	Resolved	No	No	Clinical Record
TST	Exacerbation of OA wrist pain.	Moderate	GP review. Hand physiotherapist prescribed pressure glove and wrist splint	Missed two sessions. Reduced use of UL during exercise. Closer supervision.	Resolved	Yes	No	Adverse Events report
PRST	Onset of hip pain following hip extension exercise	Moderate	Attended private physiotherapy.	Discontinued hip extension exercise. Initially did not impact ADL's or programme attendance. Elected to discontinue programme following holiday for fear of re-injuring.	Resolved	Yes	No	Adverse Events report
PRST	Fall at home.	Minor	Presented to Accident and Emergency department. The following day. Screened and discharged.	Reduction in volume and intensity of exercise for four sessions.	Resolved	No	No	Clinical Record
PRST	Chest infection.	Serious	Hospital admission.	Unable to attend 21 sessions. Elected to withdraw from research on advice of Private Hospital registered Nurse.	Resolved	No	Yes, Emphysema	Clinical Record
TST	Exacerbation of asthma	Moderate	Accident and Emergency care.	Reduced exercise intensity and volume for three sessions	Resolved	No	No	Clinical Record

TST	Knee pain	Minor	Nil	Knee pain experienced on high load weight bearing tasks such as stairs and hopping. Modified these exercises for three sessions.	Resolved	Yes	No	Adverse Events report
PRST	Back/Hip pain secondary to pushing scooter home.	Minor	GP review.	Limping when walking. Exercise intensity reduced for two sessions	Resolved	No	Yes, Back pain	Clinical Record
TST	Exacerbation of OA knee pain with sit to stand exercise.	Minor	Nil	Missed one session. Decreased amount of sit to stand activity	Resolved	Yes	Yes, OA knee	Adverse Event report

Four adverse events were reported through formal adverse events reporting channels, a further five were identified through review of the clinical records. Five minor, three moderate and one serious adverse event were recorded during the study. Three of these adverse events were deemed to be related to the intervention; two exacerbations of existing musculoskeletal pain and one new onset of musculoskeletal pain in response to an exercise. All adverse events had resolved by the end of the intervention phase.

Data Integration

Table 8-24 triangulates quantitative and qualitative data in relation to the intervention safety. Triangulation indicates demonstrates complementary data sets, where the qualitative data adds considerable depth to that provided by quantitative data.

Table 8-24 Intervention safety – Data Integration

Quantitative Findings	Qualitative Findings	Triangulation
Nine adverse events were identified, four via formal reporting and five on review of clinical records (Adverse event reports, Clinical records)	Adverse events deemed unrelated to the intervention included falls in the home, respiratory illnesses and pain secondary to over exertion. (Clinical records, Physiotherapists interviews)	Complementary
	The four adverse events related to the intervention involved new or exacerbated musculoskeletal pain in relation to a specific exercise. (Adverse events reports, Clinical record, Physiotherapists interviews, Participant interviews)	
There was one serious, three moderate and five minor adverse events. (Adverse event reports, Clinical records)	Some participants experienced negative symptoms in response to exercise which did not breach the threshold of an adverse event, including postural hypotension and musculoskeletal pain. (Clinical record, Participant interviews, Physiotherapist interviews)	
Four adverse events were related to the intervention and five were unrelated. (Adverse event reports, Clinical records)	It was challenging for the physiotherapist to manage a group of five people with stroke who had varying levels of physical disability. The physiotherapists reported that whilst the level of physical disability did not compromise safety per say, it added to the complexity of delivering the intervention. (Physiotherapist interview)	
	Managing people who had cognitive or perceptual deficits was also a challenge. (Physiotherapist interviews)	

Usual Care Control Group

Table 8-25 outlines the amount of exercise and rehabilitation activity each UCC participant completed, each week for the duration of the study in minutes. The UCC group completed, on average, 181 minutes of exercise and rehabilitation activity per week. Participants in the UCC group carried out a range of activities including home exercises, conductive education, walking programmes and swimming.

Table 8-25 UCC Group – Exercise and Rehabilitation Activity (mins)

Week	1	2	3	4	5	6	7	8	9	10	11	12	Average
1	150	135	195	105	15	150	150	90	165	320	300	270	170
2	420	420	420	60	60	240	180	420	480	450	330	450	328
3	240	200	315	295	555	325	385	280	365	375	365	365	339
4	0	0	0	0	0	0	0	0	0	0	0	0	0
5	60	30	0	60	140	120	0	60	240	60	60	80	71
Group													181

8.5.3 Outcomes

This following section presents a descriptive summary of the study outcome measures of neural plasticity, impairment, locomotor ability, participation, self-efficacy and HRQoL.

Neural Plasticity Measures

Table 8-26 provides a descriptive summary of the pre and post intervention BDNF values prior to, during and following sub-maximal exercise in the study sample and each of the respective groups along with the mean difference and 95% confidence intervals.

Table 8-26 Summary of BDNF Measures (ng/ml)

Group	Measure	Pre-Intervention		Post-Intervention		Mean Difference (95% CI)
		Mean (SD)	Range	Mean (SD)	Range	
Sample (n=13)	BASE	25.45 (10.27)	8.00 to 41.67	26.09 (8.05)	13.96 to 39.11	0.87 (-6.62 to 4.88)
	EXERCISE	32.93 (9.20)	15.42 to 44.35	31.37 (7.87)	18.44 to 44.73	-1.07 (-3.46 to 5.60)
	REST	26.02 (9.64)	4.53 to 41.02	23.79 (9.85)	5.98 to 35.46	-2.96 (-6.17 to 12.09)
STT (n=2)	BASE	29.30 (0.56)	28.90 to 29.69	36.12 (4.23)	33.13 to 39.11	6.83 (-39.80 to 26.15)
	EXERCISE	25.96 (0.62)	25.52 to 26.40	34.53 (3.83)	31.82 to 37.23	8.57 (-48.53 to 31.40)
	REST	12.11 (10.72)	4.53 to 19.69	30.52 (6.99)	25.57 to 35.46	18.41 (-51.89 to 15.08)
PRST (n=2)	BASE	25.71 (10.14)	16.12 to 36.33	22.42 (2.25)	20.83 to 24.01	-3.81 (-144.79 to 152.40)
	EXERCISE	34.50 (9.16)	26.23 to 44.35	28.72 (6.52)	24.11 to 33.33	6.57 (-49.97 to 63.11)
	REST	30.61 (9.72)	21.77 to 41.02	17.48 (9.68)	10.63 to 24.32	-17.56 (-145.53 to 180.64)
TST (n=4)	BASE	27.48 (12.48)	11.98 to 41.67	28.83 (10.19)	13.96 to 36.15	1.79 (-14.90 to 11.33)
	EXERCISE	35.18 (7.89)	23.65 to 44.16	28.46 (10.18)	18.44 to 38.02	-5.72 (-1.79 to 13.22)
	REST	26.47 (7.99)	16.98 to 36.98	18.25 (13.62)	5.98 to 34.58	9.64 (-12.29 to 31.56)
UCC (n=5)	BASE	21.74 (11.49)	8.00 to 37.27	21.36 (4.26)	14.90 to 25.10	0.38 (-13.07 to 13.83)
	EXERCISE	32.51 (12.63)	15.42 to 43.00	33.50 (8.44)	21.25 to 44.73	-1.00 (-9.63 to 7.64)
	REST	28.38 (8.12)	18.54 to 38.83	28.05 (4.50)	21.88 to 31.88	0.33 (-9.93 to 10.60)

Small sample sizes in each of the intervention groups for the BDNF measure negates any meaningful comparison of mean group differences.

Impairment Measure

Table 8-27 provides a descriptive summary of the pre and post intervention 1-RM values for the study sample and each of the respective groups along with the mean difference and 95% confidence intervals. The results indicate that all groups improved in 1-RM in the post-intervention phase, although the magnitude of the improvement is greater in the PRST, TST and STT intervention groups than the UCC group.

Table 8-27 Unilateral Leg Press 1-RM (%BW)

Group	Pre-Intervention		Post-Intervention		Mean Difference (95% CI)
	Mean (SD)	Range	Mean (SD)	Range	
SAMPLE (n=18)	63.20 (18.65)	23 to 84	85.92 (24.84)	46 to 128	21.85 (10.37 to 33.36)
STT (n=5)	71.40 (13.74)	50 to 84	88.40 (28.06)	65 to 120	17.00 (-8.53 to 42.54)
PRST (n=3)	56.60 (19.51)	28 to 74	90.00 (32.97)	69 to 128	34.00 (-33.62 to 101.62)
TST (n=5)	61.60 (22.50)	23 to 82	81.00 (21.67)	46 to 103	19.40 (4.25 to 34.55)
UCC(n=5)	70.20 (20.29)	49 to 92	79.20 (12.09)	68 to 97	9.00 (-3.72 to 21.72)

Activity Measures

Table 8-28 provides a descriptive summary of the pre and post intervention values for the planned primary outcome measure; comfortable walking speed. The results indicate that on average all groups improved in comfortable walking speed at the post-intervention assessment, although the magnitude of the improvement is greater in the PRST & TST groups.

Table 8-28 Comfortable Walking Speed (m/s)

| Group | Pre-Intervention | | Post-Intervention | | Mean Difference |
	Mean (SD)	Range	Mean (SD)	Range	Mean (95% CI)
Sample (n=19)	0.73 (0.42)	0.12 to 1.33	0.94 (0.47)	0.13 to 1.55	0.16 (-0.04 to 0.32)
STT (n=5)	0.83 (0.46)	0.14 to 1.33	0.90 (0.53)	0.13 to 1.44	0.07 (-0.06 to 0.20)
PRST (n=4)	0.79 (0.42)	0.14 to 1.29	1.11 (0.23)	0.84 to 1.41	0.16 (0.06 to 0.25)
TST (n=5)	0.58 (0.42)	0.12 to 1.04	0.83 (0.58)	0.19 to 1.55	0.26 (-0.30 to 0.81)
UCC (n=5)	0.75 (0.43)	0.23 to 1.22	0.82 (0.44)	0.25 to 1.28	0.07 (-0.02 to 0.16)

Table 8-29provides a descriptive summary of the pre and post intervention locomotor ability measures for the study sample and each of the respective intervention groups, along with the mean difference and 95% confidence intervals. On average in all intervention groups on all measures of locomotor ability the mean difference between pre and post intervention indicates an improvement, with the exception of fast walking speed in the STT group which did not change. All locomotor ability measures in the UCC got worse or did not change.

Table 8-29 Locomotor Abilities

Group	Outcome Measure	Pre-Intervention		Post-Intervention		Mean Difference (95% CI)
		Mean (SD)	Range	Mean (SD)	Range	
Sample (n=19)	30s Chair Stand (Reps)	6.53 (3.44)	0 to 11	9.34 (3.50)	0 to 14	2.36 (1.15 to 3.57)
	Fast Walking Speed (m/s)	0.93 (0.58)	0.16 to 2.02	1.13 (0.61)	0.15 to 2.03	0.12 (-0.04 to 0.28)
	Step Test (Reps)	7.13 (5.19)	0 to 15	9.29 (5.17)	0 to 20	1.16 (-0.23 to 3.52)
	Stairs Up (s/step)	2.35 (2.98)	0.58 to 10.00	1.25 (1.17)	0.57 to 4.55	-1.10 (-2.22 to 0.02)
	Stairs Down (s/step)	2.52 (3.14)	0.57 to 10.00	1.44 (1.33)	0.45 to 4.45	-1.09 (-2.15 to 0.02)
STT (n=5)	30s Chair Stand (Reps)	8.20 (2.59)	4 to 11	9.60 (2.79)	5 to 12	1.4 (- 0.02 to 2.82)
	Fast Walking Speed (m/s)	1.18 (0.71)	0.16 to 2.02	1.16 (0.75)	0.15 to 2.03	-0.01 (-0.19 to 0.16)
	Step Test (Reps)	8.20 (5.67)	0 to 14	8.40 (5.37)	0 to 14	0.20 (-1.16 to 1.56)
	Stairs Up (s/step)	2.25 (3.31)	0.58 to 8.15	1.50 (1.71)	0.57 to 4.55	-0.74 (-2.73 to 1.24)
	Stairs Down (s/step)	2.59 (3.85)	0.57 to 9.45	1.41 (1.63)	0.45 to 4.30	-1.18(-3.94 to1.59)
PRST (n=4)	30s Chair Stand (Reps)	5.60 (3.91)	0 to 9	10.00 (1.41)	8 to 11	3.00 (0.75 to 5.25)
	Fast Walking Speed (m/s)	0.98 (0.55)	0.24 to 1.78	1.32 (0.41)	1.01 to 1.89	0.16 (-0.05 to 0.36)
	Step Test (Reps)	7.20 (5.26)	0 to 13	10.75 (6.65)	5 to 20	1.75 (-3.97 to 7.47)
	Stairs Up (s/step)	1.27 (0.85)	0.75 to 2.54	0.73 (0.18)	0.60 to 1.00	-0.54 (-1.60 to 0.53)
	Stairs Down (s/step)	1.34 (0.71)	0.62 to 2.31	0.90 (0.26)	0.69 to 1.24	-0.44 (-0.32 to 1.19)
TST (n=5)	30s Chair Stand (Reps)	5.80 (3.77)	0 to 10	8.60 (5.41)	0 to 14	2.80 (-1.07 to 6.67)
	Fast Walking Speed (m/s)	0.70 (0.49)	0.18 to 1.28	0.94 (0.65)	0.22 to 1.68	0.23 (-0.30 to 0.77)
	Step Test (Reps)	6.00 (5.61)	0 to 15	9.00 (4.64)	2 to 13	3.00 (-2.34 to 8.34)
	Stairs Up (s/step)	3.31 (3.89)	0.83 to 10	1.41 (1.06)	0.65 to 3.17	-1.90 (-1.63 to 5.43)
	Stairs Down (s/step)	3.39 (3.81)	0.86 to 10	1.88 (1.57)	0.66 to 4.45	-1.51 (-4.34 to 1.32)
UCC (n=5)	30s Chair Stand (Reps)	7.00 (4.85)	0 to 11	6.00 (4.85)	0 to 11	-1.00 -2.24 to 0.24)
	Fast Walking Speed (m/s)	1.06 (0.52)	0.40 to 1.59	1.00 (0.55)	0.36 to 1.61	-0.06 (- 0.14 to 0.03)
	Step Test (Reps)	7.60 (3.05)	4 to 12	7.80 (3.56)	5 to 13	0.20 (-1.16 to 1.56)
	Stairs Up (s/step)	1.59 (0.80)	0.64 to 2.32	1.37 (0.62)	0.61 to 2.03	-0.22 (-0.65 to 0.22)
	Stairs Down (s/step)	2.40 (1.95)	0.62 to 5.46	1.79 (0.94)	0.62 to 2.78	-0.62 (-2.09 to 0.85)

Participation, Self-efficacy and HRQoL Measures

Table 8-30 Participation, Self-efficacy and HRQoL Measures

Group	Measure	Pre-Intervention		Post-Intervention		Mean Difference (95% CI)
		Mean (SD)	Range	Mean (SD)	Range	
Sample (n=19)	SIS	61.59 (23.15)	26.59 to 98.13	66.62 (21.02)	38.68 to 93.13	5.03 (-0.92 to 10.98)
	ABC	63.95 (26.16)	9.00 to 95.63	68.22 (21.32)	15.00 to 99.38	4.27 (-3.41 to 11.95)
	SIPSO	28.29 (6.96)	14.00 to 36.00	30.00 (7.48)	15.00 to 40.00	1.71 (-0.14 to 3.29)
STT (n=5)	SIS	68.96 (28.78)	32.12 to 98.13	71.37 (24.24)	39.79 to 93.13	2.41 (-4.44 to 9.25)
	ABC	63.58 (33.09)	9.00 to 95.63	68.63 (31.87)	15.00 to 99.38	5.05 (-1.83 to 11.93)
	SIPSO	27.00 (8.15)	14.00 to 35.00	29.40 (7.47)	18.00 to 38.00	2.4 (0.52 to 4.28)
PRST (n=4)	SIS	65.31 (20.80)	38.65 to 88.06	70.15 (21.87)	42.85 to 92.67	4.85 (0.02 to 9.68)
	ABC	72.00 (20.16)	43.00 to 86.88	73.91 (18.43)	47.50 to 90.00	1.9 (-6.25 to 10.06)
	SIPSO	32.00 (5.42)	24.00 to 36.00	34.25 (4.50)	28.00 to 38.00	2.25 (-1.03 to 5.53)
TST(n=5)	SIS	51.24 (19.33)	26.59 to 80.56	59.04 (19.41)	38.68 to 80.31	7.80 (-13.34 to 28.94)
	ABC	57.88 (26.72)	12.50 to 83.75	63.25 (11.97)	49.38 to 82.50	5.38 (-22.87 to 33.63)
	SIPSO	26.60 (7.02)	18.00 to 36.00	27.20 (9.09)	15.00 to 40.00	0.6 (-4.41 to 5.61)
UCC(n=5)	SIS	68.97 (20.56)	42.12 to 88.54	69.75 (18.33)	45.90 to 86.52	0.78 (-2.13 to 3.69)
	ABC	61.38 (20.52)	38.75 to 89.38	56.13 (19.66)	36.25 to 84.38	-5.25 (-19.03 to 8.53)
	SIPSO	31.20 (3.70)	27.00 to 36.00	29.20 (2.05)	26.00 to 31.00	-2.00 (-4.48 to 0.48)

Table 8-30 provides a descriptive summary of the pre and post intervention participation measures for the study sample and each of the respective intervention groups, along with the mean difference and 95% confidence intervals. In all intervention groups the mean difference in measures of participation and self-efficacy were positive. In the UCC group measures either did not change or got worse.

Data Integration

Table 8-31 triangulates participant outcome data from quantitative and qualitative data sources. Qualitative data was sourced from participant interviews.

Table 8-31 Participant Outcome- Data Integration

Quantitative Findings	Qualitative Findings	Triangulation
All participants enrolled in an intervention group experienced some gains across the spectrum of impairment, activity and participation.	Participants identified a range of gains in impairments including; cardiovascular fitness, endurance, strength, range of motion, muscle tone, and mental alertness.	Convergent
	Thirteen participants described gains in aspects of walking including speed, endurance, risk of tripping, kinematics/aesthetics, dual tasking, use of aids, and the ability to move in different directions and over different terrains.	Dissonant
	Participants also described a range of locomotor gains.	Complementary
Not all participants in an intervention group experienced gains in walking ability, as measured by CWS.	Three participants, all of whom were dysphasic, described gains in their communication ability.	Complementary
	Participants described often described gains which were not formally evaluated in a study outcome measure.	Complementary
Not all participants experienced the same magnitude of gain.	Participants often failed to describe some gains which were seen in formally evaluated outcome measures.	Dissonant
	Seven participants talked about increasing their confidence in relation to balance and walking. Some participants described gains in balance and walking confidence which were not reflected in the ABC measure.	Dissonant
	Some participants described gains in participation which were not reflected in measures of participation.	Dissonant

8.6 Discussion

The section discusses the feasibility of the main study protocol with reference to the findings of the pilot study. It addresses whether the main study protocol is considered feasible in relation to recruitment, data completeness, intervention adherence, fidelity, acceptability and safety, and makes recommendations for changes to the study protocol and interventions.

8.6.1 Study Protocol Integrity

Recruitment

The first criterion for the feasibility of the main study protocol was that 20 participants would be recruited to the study within a two month timeframe. In the first phase of recruitment, participants who were 3-9 months post stroke were targeted. The majority of potential participants were sourced from the hospital stroke services, with a few participants referred from a local physiotherapy clinic. In many cases, potential participants were deemed inappropriate to be contacted by locality staff based on their medical history as documented in the local hospital stroke register. Given that information was entered into the hospital stroke register within a few days of admission to hospital it is possible that the register may have been inaccurate or out-of-date at the time of pre-screening. This process introduced the risk that potentially eligible participants were excluded from the study inadvertently, particularly as potential participants were not formally screened by a study recruiter. Few people who were 3-9 months post-stroke approached about the study in the first recruitment phase expressed an interest in participating, consequently only two participants were recruited to the study in a two month timeframe in the first recruitment phase.

The challenges of recruitment to stroke studies, and stroke rehabilitation studies in particular, are well acknowledged [15, 435, 436]. Subsequent to the failure of the first recruitment phase failing to yield sufficient participants, a change was made to the inclusion criteria to recruit participants who were greater than three months post-stroke (with no upper limit) and alterations were made to the strategies used to engage people with stroke in the research process. It is acknowledged that by broadening the timeframe post-stroke in which the intervention is delivered, there is a risk that the treatment effect is weakened by failing to capitalise on the spontaneous recovery seen within the first 12 months following stroke [399]. However, recently the notion of a plateau in recovery in the chronic phase post-stroke has been challenged [437-439]; and as such it can be argued

that in the chronic phase post-stroke people still have considerable capacity for neural plasticity and motor learning, and that intervention may also address secondary impairments which develop as a consequence of physical inactivity.

The second phase of recruitment was far more successful with 18 participants recruited within a one month timeframe. The recruitment rate in phase two was 19% of considered participants. Previously reported studies with similar inclusion criteria report a diversity of recruitment rates ranging from 25% [34] to 51% [435]. However, there are considerable differences in the methods of recruitment and timing of screening of potential participants. In contrast to these figures, studies which screen and recruit participants in the acute phase following stroke whilst still hospital inpatients yield far lower rates of recruitment [440] but the sample maybe more representative of the stroke population than those studies which rely on rehabilitation staff and self-referral.

In the second phase of recruitment, participants were sourced from a broader referral base. Recruitment from the Stroke Foundation and local physiotherapy clinics was facilitated by face-to-face meetings with locality staff and weekly phone calls to enquire about potential participants. The importance utilising a broad range of referral sources and taking a proactive approach to working with referring organisations is emphasised in the literature [441]. In this pilot study it was not possible to embed the recruiter in locality sites, which may have yielded better recruitment rates; this is an important consideration for the main study [436, 441]. More referrals were also received via community advertising, which included local newspaper advertising in addition to the posters used in phase one, other sources of community advertising such as social media could also be considered [436]. However, referrals sourced from community advertising required more intensive screening of a greater number of people who were then deemed ineligible.

Reviews of strategies to enhance recruitment for clinical trials emphasise the importance of reducing barriers to engagement with the research process [441]. A greater proportion of those who were approached about the study in phase two were interested, suggesting that letter plus a follow up phone call was a more effective recruitment strategy than a letter alone. Reducing the burden on potential participants to engage with the research process is likely to boost recruitment, and further strategies including pre-discharge and home visits from a study recruiter could also be considered [441].

Post-intervention interviews with both participants and physiotherapists indicated that one of the reasons people volunteered for this study was the lack of options for free rehabilitation services in the sub-acute to chronic phase post-stroke. This suggests that

recruitment success in different locations is likely to be influenced by the scope of services provided through the public health system and community support services in that area. Participants' noted that their engagement was facilitated by the provision of transport, and the location and accessibility of the site. Although, it should be acknowledged that in this study, some participants elected to travel up to an hour each way to participate; addressing these potential barriers to engagement in physical activity and exercise following stroke is important [442-444]. In the main study the geographical location and transport services available at each site will be an important consideration to ensure recruitment and retention of participants.

A notable deviation from the planned study protocol was the inclusion of two participants who walked at a comfortable walking speed of greater than 1.2 m/s. The two participants had identified that they had a walking disability on screening; which they perceived would benefit from further rehabilitation. Whilst both participants comfortable walking speed exceed 1.2 m/s, they were more than 0.1 m/s below their age and height predicted comfortable gait speed [445]. The cut-off point of 1.2 m/s is therefore likely an arbitrary value which does not reflect the variance in normal walking speed with age and height, nor the walking disability that some people experience following stroke. An amendment to the inclusion criteria for the main study reflective of this is recommended.

Data Completeness

The second measure of the feasibility of the main study protocol was that data completeness exceeded 95%. Overall, the data completeness for all aspects of the study was 98%, indicating that this requirement was met.

Total data completeness for the baseline assessment phase was 98% and for the post-intervention phase was 97%. Data completeness for measures of impairment, activity and participation at baseline and post-intervention was excellent. Where data were missing it was because the participant could not complete the assessment.

Eligibility to participate in the study was determined by factors which would ensure a clinically appropriate population for the intervention. Therefore, eligibility was not predicated on suitability for either of the measures of neural plasticity. Those participants who were deemed to have a contraindication or caution to either TMS or BDNF testing were excluded from that measurement. Consequently, 65% of the sample was eligible for BDNF assessment and 20% for TMS assessment. The fact that so many participants who were deemed clinically appropriate for the intervention and consequently included in the

study were unable to participate in TMS-derived measurement of corticomotor excitability due to contraindications and precautions to the measurement tool highlights the inherent selection bias associated with the measure and limits the external validity of studies which use this tool to evaluate neural plasticity in response to locomotor rehabilitation. It will be important to acknowledge this selection bias and the consequent limitations to external validity when reporting the results of neural plasticity outcomes in the planned main study. The implications of these findings for the power of the main study power to detect change in neural plasticity are discussed in Sections 8.6.3 and 8.6.4.

Whilst only four participants were eligible to undertake TMS measurement the failure to obtain the TMS outcome measures was a significant deviation from the study protocol. This deviation reflected a decision made at the time of the pre-intervention assessment. The study protocol involved the TMS test session following the BDNF assessment. At the time of the assessment, this was deemed unfeasible given the level of fatigue participants expressed; scheduling dictated that it was not possible to include a third assessment session prior to the initiation of the intervention. The data collection schedule, therefore, requires revising to ensure adequate assessment sessions and rest time to complete all of the outcome measures. Ideally this would include three assessment sessions which could feasibly be conducted 7-10 days prior to the initiation of the intervention phase.

Data completeness for the intervention phase of the study was excellent at 100% for the intervention groups and 98% for the UCC group. The electronic format was particularly successful for ensuring completion and storage of clinical records. However, triangulation of quantitative and quantitative data revealed a number of issues which potentially influenced the accuracy of the recorded data. Two physiotherapists described how difficulties were encountered when people with cognitive and perceptual difficulties attempted to complete this documentation, for one participant this meant the information he recorded was often inaccurate with regard to both the intensity and volume of exercise he completed. The physiotherapists also noted the physical challenge for participants of carrying a clipboard between exercise stations. The STT physiotherapist elected to complete the documentation related to exercise intensity and volume on the behalf of the participants in her group. This calls into question the accuracy of this data; it was noted on review of the clinical records that there was much less day to day variability in RPE and task difficulty recorded for this group when compared to the other two groups, suggesting that this was not a true representation of the participants' experience. The documentation system requires review to ensure that the system has utility for people with stroke and that they accurately reflect the training undertaken in each session. Monitoring and

measuring intervention fidelity is paramount for the planned main study which intends to evaluate the efficacy of the interventions.

Summary

In summary, the feasibility of the study protocol was established. Recruitment data indicate that the changes made to the inclusion criteria and recruitment strategy in the second phase of recruitment were successful, and should be adopted for the main study protocol. Minor amendments to the inclusion criteria and recruitment strategy, and consideration of methods to best facilitate recruitment at each locality site are also recommended. The requirement for data completeness was achieved, although the addition of a third assessment session and modification to the clinical documentation system is required.

8.6.2 Intervention

Adherence

The main study protocol was considered feasible if the intervention adherence exceeded 80%. Overall, intervention adherence was 87%, with sessions lost due to planned absences (2%), unrelated medical conditions (7%) and related adverse events (4%). Six participants experienced medical illnesses unrelated to the intervention which necessitated an absence from the programme. For the majority of the participants, this equated to an absence of one or two sessions, usually due to winter ailments such as sore throats, colds, exacerbations of asthma etc. It is unclear whether the number of sessions lost to unrelated medical problems would have been less if the programme had been conducted in the summer months. Inclimate weather is recognised as a moderator of physical activity levels in healthy people [446]; although is not specifically mentioned as a barrier to physical activity in studies investigating barriers and facilitators to exercise and physical activity in people following stroke[442-444, 447].

Analysis of the quantitative data related to intervention adherence suggested a discrepancy in adherence between the groups, where adherence in the TST and STT exceeded 90%, whilst the adherence in the PRST group was 68%. Adherence rates in the TST and STT groups are slightly higher than those reported in other studies of task-specific training of a similar dose [103, 448-450]. When the two participants who withdrew from the PRST intervention are excluded from adherence calculations,

adherence is 93%. This rate is comparable to other trials of moderate to high intensity PRST [33, 86, 87, 451]; however when reporting of adherence rates authors do not acknowledge whether dropouts are included in adherence calculations or not. Adherence in the PRST group was particularly influenced by three participants, one of whom who had a serious unrelated medical illness (described below), another who experienced an adverse event, and a third older participant. Triangulation of quantitative and qualitative data indicated that the reasons for lower adherence in these participants were in fact multifactorial. These participants highlight the importance of multiple factors in intervention acceptability and adherence and signpost scope for improvements in the intervention design (discussed in Section 8.6.5).

The participant in the PRST group who suffered a severe chest infection, and consequently withdrew just prior to the post-intervention assessment phase was older and severely affected by her stroke. However, there were three other participants who had a similar level of physical disability and impairment who did not experience unrelated medical problems or require significant absences from the programme. Nevertheless, this participant was the only person who resided in private hospital care. It is possible that whilst this participant did meet the inclusion criteria for the study, the effect of her disability, age and frailty compounded to make her more at risk of not completing the intervention. With this in mind, review of the exclusion criteria to exclude people who reside in private hospital care is warranted.

Two participants experienced adverse events related to the intervention which resulted in non-attendance of 21 and three sessions, respectively. These adverse events are discussed in more depth below.

In summary, intervention adherence of greater than 80% was achieved in the TST and STT groups, with lower adherence in the PRST group although when drop outs were accounted for in the PRST group adherence data, adherence was 93%. Triangulation of qualitative and quantitative data revealed that adherence did not appear to relate to the intervention per se, but to multiple factors related to the individual, the group and the intervention. Therefore, the criterion for the main study protocol in relation to intervention adherence was achieved.

Fidelity

The main study protocol was deemed to be feasible if intervention fidelity in the pilot study exceeded 80%. Intervention fidelity was measured with reference to volume, intensity and progression of exercise.

Exercise volume was at or above the specified level in more than 80% of exercises in the STT (100%) and TST (97%) groups; however, in the PRST group, the specified volume was achieved or exceeded only 72% of the time. In the STT and TST groups, participants consistently achieved more than the minimum prescribed number of sets. In the PRST group, four of the five participants failed to achieve the minimum volume of exercise at least some of the time. Review of qualitative data from the clinical records indicates that this was for a variety of participant-specific reasons; one participant required prompting to transition between stations in a timely manner, another frequently completed but failed to record the second set of exercises, one participant who was moderately disabled required assistance to set up the machines and was often delayed waiting for help, and another participant experienced postural hypotension during standing exercises and required frequent rests. Given the physiotherapist's assertion that one participant usually did not record his second set of exercises despite prompting, it is likely that the specified exercise volume was attained for more than 80% of the exercises in the PRST group. However, these findings highlight issues in relation to the cognitive and physical demands of negotiating the gym environment and maintaining accurate clinical records.

Exercise intensity in each component of the intervention was designed to be moderate to high intensity and progressive, such that the participants worked harder as the programme progressed. During their post-intervention interviews, all participants described working hard during the interventions. Participants in the PRST and STT groups tended to describe the intensity of exercise as being very hard from the outset of the programme, whilst in the TST group participants described a discernible progression in intensity.

The intensity of the intervention was determined in different ways for the two components (strength and motor skill) of the programme. Fidelity was achieved in relation to RM in both the STT (89%) and PRST groups (87%). Those times when the intensity fell below the required repetitions per set tended to be at points of progression in the programme, where a new RM was being established. This finding was reinforced by the physiotherapists' descriptions of the strategies required to find the new RM with different participants. The required RPE for the final repetition was >18 on the Borg scale.

This was achieved in 85% of the exercises in the STT group but only 51% in the PRST group. However, in most cases, the participants in the PRST group rated their exercise as 18 or 17 on the Borg scale, suggesting they were at or near their RM. There is considerable ongoing research describing the relationship between RPE and various parameters of strength training, however the most effective method of utilising RPE to monitor and set training intensity in healthy adults has yet to be agreed [230, 452-454]. The Borg scale has not been validated for use in lower limb resistance training in a stroke population, although recently a small study validated its use in the upper limb in people with chronic stroke; demonstrating that these participants exerted similar %1-RM loads at different RPE to healthy participants [455] This finding has also been replicated in people with Multiple Sclerosis [456], suggesting that RPE is likely a valid tool to determine strength training intensity in people with neurological pathology, although further research is required. As participants' 1-RM were not re-assessed during the programme it is not possible to validate whether the training loads utilised were comparable to the predicted %1-RM, however the RM sets were achieved and intensity of training and load increased progressively over the programme. It should also be noted that it was difficult to achieve the specified intensity during the dorsiflexion exercise; alternative modes of exercising these muscles require consideration.

In the task-specific training component, exercise intensity was set based on the perceived difficulty of each task, such that the participant aimed to be working at a specified level of difficulty, which increased as the programme progressed. The percentage of exercises conducted at the specified task difficulty was 94% in the TST group. In contrast, in the STT group, just 37% were conducted at the specified task difficulty and 55% of exercises were above. In this intervention group, the guidelines in relation to exercise intensity did not appear to be followed; task-specific training should have been progressed from 'Somewhat Difficult' to 'Very Difficult' in a step wise manner from Week 3 to Week 9. However, the participants in the STT group tended to be working at a 'Very Difficult' level from Week 3 onwards. The rating of task difficulty did not appear to correlate or coincide with the number of task difficulty progressions made, suggesting that task difficulty was not utilised as a measure by which exercise progression was driven. It is not clear whether these limitations in treatment fidelity relate to inaccurate documentation or a failure to follow the training manual correctly, but they do highlight the importance of more rigorous quality control and clinical supervision mechanisms for the duration of the intervention in the main study to ensure that treatment fidelity is maintained.

Analysis of clinical records indicates that all three intervention groups met the requirement to progress the exercises over the duration of the programme. In the strength training component, the percentage of change in load from the beginning to the end of the programme indicated that the progression was achieved and was similar between the groups. However, post-intervention interviews indicate that individual participants increase in load over the intervention programme was influenced by various factors including; co-morbidities, fatigue and reluctance to exercise at high intensities. In the task-specific training component the TST group had, on average, 60% more progressions per participant, than the STT group. Review of the clinical records suggests that there were a number of differences in exercise progression between the STT and TST groups. Some of these differences may have related to a failure to follow the training manual directions, particularly in relation to the introduction of secondary tasks from Week 5 and random practice structure from Week 9, but they may also relate to limitations imposed by the STT programme. As discussed below there were challenges in safely supervising participants utilising corridor and outdoor spaces; this was especially relevant in the STT group where the participant began their exercise at a strength training station in the gym. In the main study careful consideration of the exercise environment at each locality site is therefore required to ensure that the environment is conducive to implementation of the STT intervention as prescribed. It should be noted that both the TST and STT physiotherapists described feeling well prepared for carrying out the intervention and well supported throughout, indicating that whilst the STT physiotherapist felt confident with the intervention programme more rigorous quality control and clinical supervision is required to ensure intervention fidelity is attained.

Triangulation of data sourced from the clinical records indicated that in many cases when treatment fidelity was not achieved, it was a justifiable modification to the intervention in response to negative symptoms experienced by the participant. These negative symptoms included postural hypotension and musculoskeletal pain. In addition to those negative symptoms documented by the physiotherapists, some participants described how they could not work hard enough during the intervention or how their progress was hampered by co-morbidities, particularly musculoskeletal pain. The monitoring and management of negative symptoms are discussed in more detail in below.

In summary, whilst treatment fidelity was achieved in all three interventions, there are some disparities between the groups which relate the rigour with which the training intervention was applied and with which documentation accuracy was maintained.

Safety

The interventions were deemed safe if adverse events were at or below rates previously described for people with stroke when exercising. Intervention safety was evaluated by triangulating adverse event reporting, review of clinical records and post-intervention interviews with the physiotherapists and participants. Adverse event reporting indicated that there were no fatal adverse events in any group, nor were there any second strokes or cardiac events. This is in keeping with previously published reporting of adverse events in response to exercise in people with stroke which indicate that exercise is a safe and low risk intervention in medically stable people with stroke [457].

Four reported adverse events were deemed to be related to the intervention; three in the TST group and one in the PRST group. In each case, the participant experienced new or exacerbated musculoskeletal pain in relation to a specific exercise. Two were moderate adverse events, where the participant required input from a health professional and ongoing modification to the intervention to ensure that they did not re-injure or exacerbate their condition. The other two were mild, where the pain resolved within a week and modification to the intervention was minor. In all cases, the pain was resolved by the end of the intervention phase; however, for one participant, the adverse event contributed to her discontinuing the intervention. Review of the clinical records indicates that this participant was working below the prescribed intensity and at speed when the injury occurred; the physiotherapist had previously documented that the participant had difficulty grasping the purpose of the intervention and following the specified training parameters. In contrast, the other three adverse events which were related to the intervention occurred when the participant most likely developed an overuse injury in response to excessive load through a joint during an exercise.

Comparison of moderate and minor adverse events rates to other studies is challenging, as many authors do not monitor or describe moderate and mild adverse events [103, 458]. Those studies which do provide more comprehensive descriptions of adverse events report rates of between 20-40% [35, 440, 450] although definitions of what constitutes an adverse event vary considerably. The rate of adverse events reported through formal adverse event reporting mechanisms in the current study was 27%. However, when adverse events identified through review of clinical records are included the rate is 53%, with 20% of participants experiencing an event which was related to the intervention. It is likely that adverse events rates in the current study are not higher than previous studies but a function of differing definitions and more rigorous identification methods in the current study [459].

Research into adverse events reporting indicates that no one method of reporting is likely to elucidate all adverse events [460]. Whilst the process for adverse events reporting by the physiotherapists requires some modification to ensure that all events are formally reported, there is also scope to gain more robust data by using multiple methods of reporting adverse events such as review of clinical records and participant self-report [461]. As the UCC group were not contacted to identify adverse events no comparison can be made to adverse events in this group. In the main study it will be important to include a mechanism for identifying adverse events in the UCC group.

The clinical records were also reviewed to identify negative symptoms in response to exercise which did not breach the threshold of an adverse event. The clinical records indicate that two older participants experienced postural hypotension, as determined by the treating physiotherapist. Both participants required modification to the intervention to accommodate this. It is worth noting that whilst a pulse oximeter and sphygmomanometer were available for use, the clinical record indicate that neither physiotherapist elected to use these tools to monitor their participants. Although exercise interventions may result in a medium and long term decrease in cardiovascular risk factors in people with stroke [462], the immediate effect training is cardiovascular stress. In both healthy adults and those with cardiac pathologies strength training causes an immediate increase in both diastolic and systolic blood pressure and heart rate; the magnitude of which is a function of the percentage of 1-RM, the muscle mass being worked, the duration of the contraction and rest periods, and whether the person attempts to utilise a Valsalva manoeuvre during the exercise [463, 464]. It is assumed that similar cardiovascular stress is experienced during strength training in people with stroke, although no studies investigating this were identified. Studies evaluating cardiovascular stress during standard physiotherapy including task specific training indicate that these types of interventions do not routinely impose significant cardiovascular stress [465, 466] even during advanced walking tasks similar to those used in the STT intervention [467]. Given the physiotherapists failure to adequately monitor cardiovascular response to the intervention in participants who experienced negative symptoms, stronger guidance in relation to the monitoring and management of cardiovascular stress during the training is warranted [464, 468].

Graded exercise testing with ECG as part of evaluation prior to beginning an exercise programme in people with stroke had previously been advocated prior to the development of this intervention with a number of caveats regarding the risks associated with the testing itself, the suitability of testing methods for people with stroke who have

significant physical disability and the pragmatics of access to such testing services[80]. Given the relatively low risk associated with exercise following stroke, the fact that the intervention was not designed as a cardiovascular endurance training programme and that graded exercise testing is not routine in the New Zealand healthcare context in either the stroke population or in people with cardiac pathologies referred for cardiac rehabilitation, a more pragmatic approach to clinical decision making with respect to cardiovascular safety for exercise was adopted. This included consultation with the potential participants' primary health care provider, screening and exclusion based on absolute contraindications to exercise and the identification of relative contraindications and precautions to exercise. Since the piloting of this intervention the value of graded exercise testing has continued to engender considerable debate in the clinical literature, with recent guidelines offering differing views [468, 469]. This issue will require continued monitoring as more evidence regarding the relative risks and benefits of exercise interventions in people with stroke and the evaluation of cardiovascular risks comes to light

In addition to the four adverse events related to the intervention, a further four participants, one in the STT group and three in the PRST group experienced short duration musculoskeletal pain which did not impact ADLs nor require input from a health professional, but required some modification to the intervention. Three of these participants had documented pre-existing musculoskeletal pain and the pain in response to the intervention represented an exacerbation. In addition, a further two participants described during their post-intervention interviews how their osteoarthritis (OA) limited their participation or the magnitude of gains they received from the intervention. OA is common in middle aged and older adults and is a frequent co-morbidity seen in people with stroke [470]. Exercise is strongly recommended in guidelines for the management of OA and the recommended training parameters of the interventions in this study were in keeping with those recommended for people with OA [471]. However, whilst the physiotherapists were informed of participants pre-existing health conditions and precautions to exercise, the progression of exercises was not specifically symptom limited in people with musculoskeletal pain. Consequently, there is a risk that these participants were exercising at an intensity which exacerbated their pain. It is therefore recommended that in people with stroke who also have musculoskeletal pain, exercises are progressed in relation to intensity only when there is no increase in baseline pain in response to the intervention.

The physiotherapists' interviews also highlighted the challenge of managing a group of five people with stroke with varying levels of physical disability. Each group was balanced for age and physical disability through the minimisation process (refer to Section 8.4.4) resulting in an even spread of physical disability across the groups. The physiotherapists reported that the level of physical disability did not compromise safety per se, but it did add to the complexity of delivering the intervention However, in some groups this challenge appeared compounded by managing people who also had cognitive or perceptual deficits. Participants who had cognitive and perceptual deficits often required frequent prompting, closer supervision and assistance to remember, follow and record their response to the intervention. Whilst cognitive deficits were screened using the MMSE and significant cognitive deficits were an exclusion criteria, it appears that more sensitive evaluation of cognitive and perceptual impairments is required [472]. The MMSE has been criticised for failing to detect more mild forms of cognitive impairment, particularly impairments in executive function and perception [473]. It is also recommended that cognitive function be used as a factor for minimisation, in addition to walking speed, as the participants' ability to engage with the intervention appeared to be significantly influenced by cognitive impairment and this is likely to influence participant safety and motor learning in a group context.

In summary, adverse event reporting indicated that the interventions were safe with no fatal adverse events and no serious adverse events related to the interventions reported. The triangulation of qualitative and quantitative data provided considerable depth to the understanding of intervention safety. Highlighted issues include; methods for adverse event reporting, the risk of minor adverse events and negative symptoms in response to training and the influence of cognitive and perceptual impairment on intervention safety.

Acceptability- Participants

One of the criteria for acceptance of the main study protocol was that the interventions were deemed acceptable by the participants and the physiotherapists. This criterion was met, with both the participants and physiotherapists describing a high degree of acceptability. The relative acceptability or perceived value of the interventions for participants appeared to be mediated by a number of broad and inter-related factors, including making progress, sourcing motivation, working hard, the people, and the fit with the individual and their lifestyle. These themes, describing factors which enhanced intervention acceptability, align well with the literature describing facilitators to physical activity and exercise in people with stroke [442, 444, 447, 474, 475].

A sense of success with the intervention, the identification of gains in response to the intervention which extended beyond activity to gains in participation and confidence appeared strongly related to the intervention acceptability. An understanding and recognition of the benefits of exercise following stroke is recognised as a facilitator; conversely a perception that exercise will not make a difference or could be harmful following stroke acts as a barrier to engagement in physical activity [443, 447, 474, 475]. Being able to clearly identify the specific benefits of the intervention for themselves appeared to enhance intervention acceptability for participants.

All participants referred to different sources of motivation which encouraged their initial engagement with the programme and then supported their continued participation. The value of motivators, both internal and external, feature strongly in the literature describing barriers and facilitators to physical activity following stroke [443, 447, 474, 475]. In this study, whilst external motivational factors were relevant to the acceptability of the intervention, self-motivation appeared to be a much more powerful moderator. Those who described high levels of self-motivation and self-determination were more likely to view the intervention positively. In contrast, some participants who had lower levels of adherence and found the intervention less acceptable had external motivators for engagement

Participants described the importance of the others in promoting intervention acceptability; this included the other members of the intervention group, family and the health professionals involved. The other members of the group were particularly powerful and the group acted as a source of obligation, inspiration, and support. Exercising with a group of people with stroke is described as a potentially powerful facilitator of exercise activity in people following stroke [447, 474]. Qualitative data indicates that a strong positive group dynamic developed quickly within most groups despite considerable diversity in age, level of disability, ethnicity and social situation. In contrast, the disruptive nature of negative group interactions was seen in the PRST group at times, likely influencing intervention acceptability for members of this group. Post-intervention interviews indicated that the structure of the intervention sessions was such that there was very little time and scope for social interaction, suggesting that the intervention structure did not strongly support positive social interactions.

Participants frequently described the level of physical and cognitive effort required to complete the interventions, and reported fatigue in response to the programme. Qualitative studies investigating barriers and facilitators to exercise and physical activity

after stroke highlight that low energy and fatigue are potential barriers [443, 447]. However in this study, where participants were already engaged in an exercise programme, the experience of fatigue was not considered a barrier to engagement, possibly because participants were aware of a reduction of fatigue and increase in energy and capacity, as the programme progressed. In many cases the intensity of the intervention and the level of effort required to participate appeared to highlight to participants a capacity for activity which they had previously been unaware of, seemingly increasing self-efficacy. Whilst many participants made the link between their level of effort and the gains they got from the intervention, this was not explicitly outlined to participants, nor was the rationale for the intervention and its training parameters justified.

The extent to which the intervention fit with the individual and their lifestyle also influenced acceptability. The relative disruption of the intervention to the participant's lifestyle appeared to be strongly influenced by how important they perceived the intervention. For the most part, the intervention aligned well with the participants' desire to improve their locomotor ability. However, some participants had other physical issues which were not addressed as part of the intervention and this appeared to influence intervention acceptability. For example, those with significant upper limb impairment, people with bilateral symptoms, significant co-morbidities and those with few social supports to enable transfer of their new skills to their home environment all described how the intervention had, in part, failed to meet their needs.

Whilst a comprehensive review of theoretical models of behaviour change in relation to physical activity in people with stroke are considered beyond the scope of this thesis [476, 477], participant interviews provide a wealth of information about factors which promoted or challenged intervention acceptability. Many of these factors relate to strategies which support behaviour change and facilitate engagement in physical activity and exercise. These factors provide sign posts for the refinement of the intervention. The importance of self-motivation to intervention acceptability suggests a need to utilise strategies which enhance self-motivation and determination. Strategies such as: education about the benefits of exercise, individualised goal setting and celebration of successes may encourage and promote self-motivation and self-efficacy [476, 478-480]. Education in relation to the rationale for the intervention, and in particular the rationale for the intensity of training may further promote acceptability and enhance engagement, rather than relying on participants to draw these conclusions independently [476, 478]. More explicit promotion of positive group social interactions may also be warranted [476]. The

scope to further address individuals' specific physical issues and barriers to translation of gains to their home environment are also worth consideration.

Acceptability-Physiotherapists

The criterion of physiotherapists' intervention acceptability by physiotherapists was met for all three interventions, although the highest level of acceptability was reported by the TST and STT physiotherapists. In contrast the PRST group physiotherapist, whilst positive, was more judicious in her discussions. However the relative acceptability of the interventions did not appear to relate to the intervention per se but to a number factors which were seen across the intervention groups; with different factors playing a greater or lesser role in intervention acceptability for different physiotherapists. The themes which appeared to influence intervention acceptability for the physiotherapists included; seeing the participants improve, the logistics of delivering the interventions, developing new ways of working with and having new understandings of the capabilities of people with stroke.

The physiotherapists described, at length, the gains which the participants in their groups achieved during the intervention. They primarily reported gains in activity, although there was some focus on gains in impairment, participation and confidence. The TST and STT physiotherapists described a greater breadth of gains compared to the PRST physiotherapist. This did not appear to be related to group differences in participant outcomes, but may have arisen from the physiotherapist's awareness of participants gains as the PRST physiotherapist had less opportunity to observe the participants undertake locomotor skills as part of the intervention. The physiotherapists often did not identify all the gains participants achieved, as measured by the study outcome measures and they often did not identify the extent of participation gains identified by participants

The physiotherapists raised a number of issues which focused on the practicalities of implementing the intervention with their group. Refinement of the interventions which address the high level of support and clinical supervision required at the beginning of the intervention, balancing of the groups in relation to both physical and cognitive disability, refinement of the circuit timing, and changes to the documentation processes are all likely to enhance acceptability for the physiotherapists.

All of the physiotherapists described how the intervention challenged them to work in new ways. One key difference the physiotherapists described from their normal practice was the requirement of the intervention to progress exercises based on intensity rather

than on the quality of the participants' movement. Whilst evident across both components of the STT intervention, this issue was referenced most in relation to task-specific training. It has previously been suggested that physiotherapists are overly precautionary in their rehabilitation of people with stroke [457, 481]. The tension between quality of movement and intensity of training highlights the likely role of the therapists' theoretical framework for clinical decision making in the relative acceptability of the interventions. The design of the interventions was based on research evidence related to strength and task-specific training with reference to neuroscience and motor learning literature (Refer to Section One: Intervention Development); no reference was made to the literature around the Bobath approach. The Bobath treatment paradigm is very focused on the concept of quality of movement and the use of handling and facilitation techniques to improve motor performance [482]. The use of handling and facilitation techniques to improve motor performance during motor skills is also somewhat at odds with concepts of motor learning which promote the use of intrinsic feedback and the experience of errors to promote motor learning in both normal and neurological populations [222, 223]. Regardless of the level of evidence to support a focus on quality of movement during the intervention, this tension potentially influences intervention acceptability for physiotherapists and therefore may impact intervention fidelity and represent a barrier to translation into clinical practice [483-485]. It is also worth noting that for most neurological physiotherapists, whilst the construct of neural plasticity underpins their clinical practice much of the evidence from neural plasticity literature has highlighted the importance of dose of training to achieve gains in people with stroke [486], meaning that the focus has often been on increasing the number of repetitions of an exercise. However, more recently the importance of intensity of training has been emphasised [487]. Physiotherapists concerns about the emphasis on training intensity at the expense of movement quality could be addressed by spending more time during the physiotherapists training justifying the intervention rationale. However, the feasibility of engendering a change in a physiotherapist's theoretical framework for clinical decision making in such a short period of time is questionable. Alternatively, incorporating strategies which enable greater consideration of quality of movement during the intervention may be warranted, provided they do not influence other training parameters considered important to intervention fidelity. Given that physiotherapists utilise multiple sources of evidence to guide their clinical practice, much gained during the interaction with patients, this may be a more successful approach [488]. This is reinforced by the fact that all the physiotherapists described how participating in the intervention had challenged their beliefs about the capacities of people with stroke and resulted in a change in their clinical practice.

The requirement to modify and progress the interventions was considered one of the advantages of the interventions that enhanced the acceptability for physiotherapists. All of the physiotherapists described the strategies they utilised to modify the participants' exercises to achieve the desired intensity of training. Based on the physiotherapists' feedback, more instruction in relation to the different strategies which can be employed to ensure participants achieve the correct intensity of training in the PRST component is required.

The group nature of the interventions appeared to be a powerful modifier of intervention acceptability for all physiotherapists. The physiotherapists took pleasure in working with a group of people and watching the group grow and develop as the intervention programme progressed. However, they each noted the challenge of working with a group of people and the need to contribute to and manage social interactions between group members. When group interactions were negative, this was a marked challenged to the intervention acceptability for the physiotherapist. Given the power of the group interactions to modifying intervention acceptability for both participants and physiotherapists, it would seem appropriate to offer better preparation to physiotherapists to support positive group interactions and to formalise this process as part of the intervention. The importance of the group is frequently acknowledged in studies of group based exercises in people with stroke [447, 474], however there has been little discussion about the role of the physiotherapist in supporting positive social interactions.

One of the challenges identified by all the physiotherapists was the need to balance the requirements of individual participants against the needs of the group. The physical dependency of the participants influenced how quickly and how much assistance people required when moving from station to station. At times, more severely affected participants slowed the progression of other participants through the stations. Greater scope to capitalise on the use of empty stations around more dependent participants is warranted to ensure that other participants are not slowed by the speed and degree of assistance more dependent participants require. At each treatment site, consideration of the environment for task-specific training should be given, including the accessibility of spaces and the capacity for two staff members to observe participants at all times. This feedback also reinforced the need to balance group with respect to physical and cognitive disability.

In summary, physiotherapists described the interventions as acceptable. Their feedback elucidates potential changes to the interventions which may enhance intervention acceptability. Qualitative data from the physiotherapists also highlighted the differences between the three interventions, which were developed based on the research evidence base and the theoretical framework from neuroscience and motor learning literature, and current clinical practice.

Usual Care Control Group

The UCC group returned monthly calendars of the organised exercise and rehabilitation activities which included a description of the activity and its duration. The average amount of exercise and rehabilitation was 181 minutes per week. This is considerably more physical activity than previously reported in the research literature [489] and is a comparable volume of exercise to the intervention groups. Although, the data collected provided no indication of the intensity at which the control participants were exercising; this information should be collected in the main study to enable comparison with the intervention groups. It may be that participants elected to initiate new activities in response to being randomised to the UCC group or represents a selection bias in exercise and rehabilitation studies.

Summary

In summary, this pilot study has established the feasibility of the STT intervention by confirming high adherence and fidelity to the intervention training parameters. Intervention safety is comparable to other trials investigating exercise in people with stroke and intervention acceptability to both participants and physiotherapists has been confirmed.

8.6.3 Participant Outcomes

As this was a pilot study, designed to assess the feasibility of the study protocol and not powered to detect differences between the intervention groups there was no formal statistical assessment of clinical efficacy. However, one of the intended aims of this study was to establish the magnitude of difference values and variance estimates of the outcome measures. However, review of the individual and group participant outcome indicates that the sample size of five per group was insufficient to estimate magnitude of difference or variance with any surety. This is particularly true given the intention of the study to recruit a sample considered represent of the population, which resulted in a very

heterogeneous sample, and the STT physiotherapist's failure to follow the training programme rigorously. Therefore this aim was not addressed by this pilot study.

Due to the small number of participants in each group eligible for BDNF measurement, it is difficult to make comment on the response of BDNF to the interventions. However, given that all members of an intervention group (STT, PRST and TST) all exercised at a moderate to high intensity for the duration of the programme there was no indication of a mean difference from pre- to post-intervention in any of the groups, or the three groups combined suggesting that magnitude of change in response to the exercise rehabilitation is unlikely to exceed the within subject variability in BDNF measures described in Chapter 6.

Results indicate that muscle strength improved in all groups; the magnitude of improvement was small in the UCC group and likely represents a learning effect [416], whilst in the intervention groups the greatest mean difference was seen in the PRST group, whilst the STT and TST groups had similar gains. Triangulation with qualitative data from the participant interviews highlights other changes in body system structure and function which were not evaluated with an outcome measure. Participants described gains in cardiovascular fitness and endurance, range of motion, muscle tone, and mental alertness. Most commonly reported of these were gains in cardiovascular fitness and endurance, which were reported by seven participants. Given that cardiovascular endurance is an important predictor of community locomotion and risk of recurrent stroke [46, 413, 490], this suggests that cardiovascular endurance should be measured in response to the intervention.

Group and individual results suggest that all participants enrolled in an intervention group experienced some gains in measures of locomotor ability. In contrast to the intervention groups, participants in the UCC group did not demonstrate an improvement on any of the activity outcome measures of greater than 10% of the baseline value. The magnitude of change in locomotor ability measures seen in the intervention groups was much greater, with the greatest gains seen in the TST and PRST groups. Whilst it is important not to over analyse the group results, it is worth noting that the fidelity of the intervention was called into question in the STT group due to potentially inaccurate recording of the participants' training and the physiotherapist's failure to follow the training programme accurately.

Not all participants in an intervention group experienced gains in the planned primary outcome measure for the main study, comfortable walking speed. The magnitude of gains seen in this measure ranged from no change to a participant who walked at 0.49m/s at baseline to 1.55m/s at post-intervention. In contrast another participant walked at

0.12m/s at baseline to 0.19m/s at post-intervention, yet moved from using a gutter frame to using a walking stick. Qualitative data from the post-intervention interviews revealed that participants experienced a diverse range of gains related to walking in aspects other than speed along with a wide range of other locomotor abilities.

The triangulation of quantitative and qualitative data in this pilot study calls into question the appropriateness of identifying a single measure of one aspect of one locomotor ability as a primary outcome measure for the STT intervention. As a complex intervention designed to improve locomotor ability over the breadth of skills required to be independent in the home and community it is expected that the STT intervention effect would extend over the breadth of locomotor skills and across the domains of the ICF model, as was reflected in the participants' post-intervention interviews. No single outcome measure was identified which adequately captured the extent of effects seen in response to the intervention. The identification of valid, reliable and sensitive outcome measures to measure the effect of rehabilitation interventions continues to be a challenge. The failure of some rehabilitation trials to display conclusive support for an intervention can often be traced to the inadequacy of any single outcome measure to account for the spectrum of changes effected in the individual. The purpose of identifying a primary outcome measure is to ensure the internal validity of the study, yet it remains to be seen if this method of analysing the response to rehabilitation interventions is the most appropriate.

8.6.4 Recommendations for Modification of the Main Study Protocol

The study protocol was considered suitable for replication in a large randomised controlled trial. Based on the findings of this pilot study a number of minor amendments to the study protocol are recommended; these amendments are outlined below Table 8-32 and Table 8-33 which addresses amendments to the methods and Table 8-34 with addresses amendments to the intervention.

Table 8-32 Modifications to the Study Protocol- Recruitment, Randomisation and Assessment

Refinement	Details	Rationale
Amend eligibility criteria	Have experienced a single disabling stroke **more than 3 months prior.** **With a gait speed more than 0.10m/s below their age and height derived predicted normal gait speed**	To widen eligibility to those include people who are in the sub-acute to chronic phase following stroke and have a locomotor disability.
Amend exclusion criteria	They had a moderate to severe cognitive deficit (**MoCA Score <22/30**) **They reside in private hospital care**.	A number of participants were included in the study that had moderate cognitive and perceptual impairment which was not identified by the MMSE. This influenced the physiotherapists' management of these participants and the participants' engagement with the intervention. Whilst a participant may meet the inclusion criteria for the study, the need for private hospital level care reflects a significant level of physical and/or cognitive disability and frailty which indicates that the intervention will place too greater burden on the individual.
Amend the recruitment strategy	Adopt the recruitment strategy used in the second recruitment phase. Employ recruiters to study staff to work onsite at locality organizations', where feasible.	A greater proportion of those who were approached about the study in phase two were interested, indicating that a more proactive recruitment which reduced barriers to engagement was effective. The development of strong community networks and liaison with locality organization staff resulted in better recruitment. Onsite recruiters may mitigate the potential bias with pre-screen exclusions.
Amend the minimization protocol	Include the degree of cognitive impairment in the minimisation protocol. Incorporate MoCA scores into minimisation protocol.	Physiotherapists described the challenge of managing people with mild cognitive and perceptual impairments. In clinical practice physiotherapists would routinely balance a group based on both physical and cognitive disability to ensure a manageable clinical case load.
Assessment scheduling	Schedule the sessions on alternate days over 7-10 days.	Participants were fatigued by the assessment sessions.

	Remove BDNF as an outcome measure.	Reliability study indicated that BDNF measures have poor to moderate reliability and significant within subject variability in people with stroke. Based on the pilot study the magnitude of response in BDNF to the intervention is unlikely to exceed the within subject variability of the measure. TMS was deemed the most suitable measure.
Amend the outcome measures selected.	Add the following outcome measures of locomotor ability; • 6-minute walk test to measure cardiovascular endurance [491] • Dual task ability test to measure dual tasking capacity during walking [492] • 12-item walking scale to measure walking self-efficacy [493]	The breadth of gains described by participants was not fully captured by the outcome measures selected.

Table 8-33 Modifications to the Study Protocol- Intervention Phase

Refinement	Details	Rationale
Enhance the physiotherapists training resources.	Provide physiotherapists with video demonstrations of intervention exercises including modifications and progressions	Supplement physiotherapist training and programme manual to improve physiotherapists' preparation for the intervention.
	Provide more advice on techniques for establishing a RM.	Achieving the required intensity of training was challenging in the PRST component. The physiotherapists were less familiar with methods to determine a RM.
Augment biographical details given to physiotherapists.	Record video of locomotor ability outcome measures taken at Baseline Assessment, attach to biography for each participant.	As it is not feasible for physiotherapists to complete a full assessment of each participant prior to commencement of the program this will improve physiotherapists' preparation for first few sessions.
Improve management of negative symptoms	Increase information provided during the physiotherapists training in relation to musculoskeletal pain and cardiovascular symptoms in response to exercise	Whilst not always deemed an adverse event, musculoskeletal pain in response to exercise is potential challenge to engagement with the intervention. Advice from OA exercise prescription literature [471] suggests that exercise intensity should not be increased where exercises increase a participant's pain from baseline.
	Develop specific procedures for documenting, monitoring and modifying the intervention in response to musculoskeletal pain and cardiovascular symptoms.	Negative cardiovascular symptoms in response to exercise were documented in the clinical records, however there was no evidence of monitoring of symptoms beyond patient report, nor were adverse event forms completed in relation to these. This represents a potential safety risk.
	Monitor heart rate and blood pressure prior to intervention.	Physiotherapists' management of participants with cardiovascular signs and symptoms requires more rigorous control to ensure best practice [462].

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Modifications to intervention programmes	Refer to Table 8-34 for details	Refer to Table 8-34 for details
Enhance intervention quality control	Undertake more rigorous monitoring of intervention fidelity during the intervention phase by regular analysis of clinical records to check that the intervention protocol is being followed and that documentation is accurate	One physiotherapist did not rigorously follow the specified programme.
Amend adverse event reporting systems	Formalize multiple avenues for adverse events reporting including; formal adverse event reporting, monthly telephone calls to all participants, self-report and clinical record review.	Multiple avenues of reporting are more effective at providing a comprehensive picture of adverse events.

8.6.5 Recommendations for Modifications to the Interventions

Recommendations for refinement to the STT intervention have been based on whether changes could be made which may mitigate any negative moderators of acceptability or enhancement of factors which promote acceptability for either the participants or the physiotherapists. Recommended changes include alterations to the intervention structure, incorporation of strategies aimed at increasing self-motivation, self-efficacy and positive group social interactions. Individualisation of the interventions will be facilitated through formalised monitoring of musculoskeletal pain and cardiovascular symptoms, the incorporation of upper limb tasks during locomotor training, formalised processes for addressing ongoing physical concerns and enhancing the transfer of locomotor abilities and physical activity behaviours to the home and community environments.

Table 8-34 Modifications to the Intervention

Aspect of the intervention	Refinement	Details	Rationale
Structure	Change the timing of each session	15 minutes social interactions/education/re-assessment/focus on technique and 45 minutes exercise	To enhance opportunities for social engagement, education and strategies aimed at increasing self-motivation and self-efficacy. Shortening the exercise session will also help to maintain the balance of exercise volume between the groups as the intervention programme progresses and the RM decreases.
Structure	Increase the number of exercise stations	Include three more stations: Trunk Flexors – Getting off floor Back Extensors – Pick up and carry loads Hip Rotators – Turning	Increase the variability in the exercise sessions. Provide space for more dependent participants to negotiate their way between stations without impacting on others. Provide stations which emphasize the use of the upper limbs during locomotor tasks.
Content	Incorporate an education component in to the programme	Utilize twelve 15 minutes sessions to provide education in relation to the following topics; • Programme overview • Using equipment • Justification for treatment rationale • What is moderate to high intensity exercise? • Normal and abnormal responses to exercise • Relationship between intensity and gains • Explanation of progressions • Exercise opportunities in your community	Better support for understanding of treatment rationale. Assist patients to anchor the intervention to their goals and aspirations. Address some of the potential modifiers to acceptability such as fatigue, negative symptoms, and intensity of exercise. Facilitate ongoing physical activity, support participants in transition to community based physical activity.

Content	Incorporate a focus on 'technique' into the intervention.	At four time points during the intervention use the 15 minutes at the beginning of the session to focus on technique. Give group and individual feedback about the requirements of each exercise.	Address the physiotherapists concerns about 'Quality of Movement'.
Content	Re-assess key functional outcomes at regular intervals.	At six time points during the intervention re-assess 1-RM, 30s chair stand test and comfortable walking speed. Provide the results to the participants.	Provide frequent feedback of progress to increase self-motivation.
Content	Utilize strategies to identify and celebrate gains and successes made in response to the intervention	Utilize a personal best board and group identified weekly best effort to identify, document and celebrate impairment, activity and participatory successes and gains regularly throughout the intervention. Seek, document and celebrate feedback from family, friends and peers in relation to progress.	Enhance self-motivation, self-efficacy and engagement with the programme.
Content	Incorporate social gatherings	Formal introductory session, halfway and end point celebrations.	Encourage positive group dynamics and peer support.
Content	Increase the number of variables in TST training during Weeks 9-12	Incorporate more variables under each parameter. Specify the minimum number of progressions in the later part of the programme.	Encourage variability in practice, ameliorate participant boredom.
Volume	Change timing of transitions	Allow 45 s transition between exercise stations	Increasing the time available to transition between stations accommodates those with more severe disability and enables time for more accurate documentation. Immediate transition from the strength component to the motor skill component in the STT group ensures that the neurophysiological effects of the strength component are maximized.

Individualization	Individualize the intervention where a participant has bilateral limitations.	Where a participant has bilateral limitations, either caused by the stroke or another pathology, the strength training component should be completed bilaterally.	Intervention acceptability was challenged by a failure to individualize the intervention for those with bilateral impairments
Individualization	Incorporate upper limb tasks	Include upper limb tasks as a training parameter in TST component. Increase the number of stations to emphasize locomotor tasks which utilize the upper limbs such as carrying loads.	Intervention acceptability was challenged by a failure to individualize the intervention for those with upper limb impairments.
Individualization	Identify ongoing physical issues not being addressed as part of the intervention and address where possible	Prescribe a maximum of two home exercises to address physical issues not being addressed as part of the intervention where appropriate. Arrange referral to external health care providers where appropriate.	Intervention acceptability was challenged by a failure to address individual concerns.
Individualization	Select the time of group if possible	In the main study following randomization where there are multiple class times the participant should be offered a choice of class time.	Intervention acceptability was challenged by the fact that participants could not select a class time which best suited them.
Documentation	Simplify documentation system	A recording station will be set up alongside each exercise station. Participants will be required to document RPE/task difficulty, load and repetitions for the first set of exercises and tick a box to indicate completion of subsequent sets. Explore potential technology options for documentation.	Participants had difficulty documenting their response to the intervention due to physical, cognitive and perceptual impairments.

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8.6.6 Impact of Recent Research on the Study Findings

The STT intervention was conceived and developed in 2009 & 2010 based on the evidence base which extended to January 2010; subsequently further research has been undertaken and published in the area of strength training and task related training. This section reviews the literature up to May 2014 using the same search strategy described in Chapter 2. Only one additional study of strength training was identified, which was of moderate quality, scoring 5/10on the PEDro scale [494]. A number of other identified studies were excluded for failing to meet the criteria for review (e.g. [98, 495, 496]). The one included study had 43 participants randomised to a 12 week intervention of either high intensity strength training of the lower limbs, aerobic training or a sham strength training intervention. Whilst muscle strength improved in the high intensity strength training group and was maintained at follow-up, only a modest gain in walking speed was seen, which was comparable to gains seen in the aerobic training group. The findings of this study echo those previously reported. A number of systematic reviews and meta-analyses have also been conducted since 2010 [497-501]. These reviews support the conclusions of the systematic review of strength training undertaken in Chapter 2, highlighting that there is insufficient evidence to assert that strength training results in significant gains in locomotor ability, particularly when it is the sole form of training [497, 498, 500]. Williams and colleagues reviewed the specificity of strength training with respect to locomotor muscles and their actions, and also concluded that to date strength training in neurological populations has been insufficiently specific to locomotor function [501]. In May 2014 the American Stroke Association published a statement making recommendations for physical activity and exercise for people with stroke [469]. This guideline recommends 1-3 sets of 10-15 repetitions at 50-80% of 1-RM 2-3 days per week in people with stroke, with a gradual increase in resistance as tolerated. The STT intervention adhered to these guidelines on strength training parameters.

Four studies meeting the criteria for inclusion in the task-specific training review were identified [450, 502-504], whilst a number of other studies failed to meet the inclusion criteria (e.g. [505-509]). The identified studies included a further 550 participants with 276 randomised to a task-specific-training intervention. Two large studies with n=250 and n=151 participants respectively have been published [450, 504] and the studies extend through the spectrum of time since stroke. The quality of the available evidence was high with all studies rating 6/10 or higher on the PEDro scale.

Two of the four studies were attention and dose matched, with the other two studies using a usual care control which was not matched for either attention or dose and not well described [450, 502]. Attention and dose matched interventions included; upper limb circuit training [504] and stationary cycling [503]. Only two studies reported gains in locomotor ability in response to the intervention [450, 504]; both studies had large sample sizes and were powered to detect change in the outcomes of interest. However, the gains in favour of the task-specific training intervention were modest in both cases, with neither reporting gains which exceed the minimally clinically important difference in the walking speed [115].

Task-specific training was provided in a one on one approach in two studies [502, 503] and in a group setting using circuit training in two studies [450, 504]. The duration of training ranged from 12 weeks [450, 502] to one year [504] , with a total dose ranging from 10 to 40 hours. The two studies reporting a dose comparable to that utilised in the STT intervention (36 hours) both reported gains in locomotor ability in favour of the task specific training group, whilst those with lower doses did not. The tasks trained were comparable to those previously reported, although the detail of description of the intervention is limited. The intensity of training was not specified in three of the four studies; one study described the use of the Borg scale of RPE to set an intensity of somewhat hard to hard [502]. This is the first time subjective rating of training intensity has been utilised in the task specific training literature. Interestingly comparison of intervention intensity between the task specific training and usual care group revealed no differences in rating of perceived exertion between the groups; suggesting that the intervention was ineffective at increasing intensity of training as planned [502]. These findings suggest that if the intention of an intervention is to increase intensity of training, based on subjective rating then it needs to be greater than 'somewhat hard to hard'.

The findings of the research published since 2010, investigating task specific training, reinforce the findings of the systematic review of task specific training reported in Chapter 2. The findings indicate that task-specific training is more effective than attention controlled interventions not aimed at improving locomotor ability. However, there continues to be insufficient evidence to assert that task-specific training is more effective than other forms of physiotherapy which are aimed at improving locomotor ability. Task-specific training results in only modest gains in locomotor ability in people after stroke which generally does not exceed the minimally clinically important difference of the measures. These findings are further supported by two recently published substantial systematic reviews and meta-analyses [510, 511].

Since the conception, development and piloting of the STT intervention a few researchers have sought to evaluate combined strength and task training interventions [98, 512-515] and two randomised controlled trials are underway [513, 516]. However, none of these interventions utilise strength training to systematically prime the central nervous system prior to task-specific training. The interventions also fail to conduct both strength training and task-specific training in an evidence based manner to maximise gains in locomotor ability, often lacking relevance, specificity and intensity in training parameters [512, 514, 517, 518]. In summary, the findings of recent research echo those which underpinned the development of the STT intervention it is consequently recommended that the basic framework for the intervention and the modifications recommended in response to this pilot trial be adopted.

8.6.7 Limitations

This pilot study is potentially limited by:

- A failure to describe the participants with respect to lesion location.
- Basing the analysis on the execution of a single cycle of each of the interventions. The interpretations are strongly influenced by a single physiotherapist and a small number of participants for each group.
- Conducting the interventions at a University site rather than at a community rehabilitation, fitness centre or hospital site, as intended in the main study.
- Whilst, based on participant and physiotherapist feedback, the method used to determine the intensity of training in the TST component has face validity; no other psychometric properties have been established for this tool.
- The primary researcher was unblinded to the allocation of three participants by virtue of the study location and the small size of the study team.

8.6.8 Implications for Future Research

This mixed methods randomised controlled pilot trial demonstrated the feasibility of the study protocol and the acceptability, feasibility and safety of the STT intervention for a powered randomised controlled trial with minor amendments to the study protocol and intervention. However, it did not establish the magnitude of difference scores or variance estimates for the outcome measures with any surety. Therefore, the next step for this research programme is the establishment of the magnitude of difference scores and variance estimates for the outcome measures in response to the STT intervention.

The qualitative data from the PRST and TST physiotherapists indicated that these interventions were a considerable deviation from standard clinical practice when working with people with stroke. These physiotherapists described the TST and PRST interventions as being of a greater volume and higher intensity than they would routinely use in clinical practice. Therefore it is recommended that the next phase of this research programme is to undertake a pilot study which compares STT to an attention and dose matched standard clinical practice intervention. This comparison would enable characterisation of the anticipated magnitude of change on relevant outcome measures, including TMS-derived measures of neural plasticity.

Comparison between the STT intervention and attention and dose matched standard clinical practice would also provide an opportunity to investigate subjective and objective measures of training intensity, such as RPE and HR. This is important as little is known about the perspectives of people with stroke with regards to training intensity or whether intensive strength and task specific training interventions such as the STT intervention impose a significant cardiovascular load. It is also recommended that future research focuses on validating and establishing the reliability of the tool developed for this study to evaluate the intensity of task-specific training.

This next phase of pilot testing should be conducted in a community rehabilitation, fitness centre or hospital site to investigate the feasibility of conducting the intervention in a clinically relevant environment. It should also consider the intervention acceptability following refinement of the intervention based on the modifications described in Table 8-33 and Table 8-34.

8.7 Summary

This mixed methods randomised controlled pilot trial has provided a rigorous and structured analysis of the feasibility of the research protocol for testing the intervention in a randomized controlled trial. Based on the findings of this pilot study the sampling and recruitment strategy, protocol integrity and the feasibility, safety and acceptability of the STT intervention have been established. However the magnitude of difference scores or variance estimates for the outcome measures have not been established. Therefore, it is recommended that the research programme progress to a pilot study which considers the magnitude of response to the STT intervention in comparison to standard clinical practice, prior to conducting a powered RCT to establish if the combined STT intervention is more effective than a single component (PRST or TST).

INTEGRATED DISCUSSION AND CONCLUSION

Introduction

This thesis has described a rigorous and structured approach to the development of a novel intervention to improve locomotor ability following stroke utilising the MRC recommendations for the development of complex interventions [388]. This process included pre-clinical intervention development, the identification of a reliable measure of neural plasticity in response to locomotor rehabilitation and pilot testing of the intervention.

Intervention Development

The grounding of the intervention development in systematic reviews of the evidence base and a narrative review of the neuroscience literature is a notable strength. By undertaking two systematic reviews of the evidence base it was identified that strength training results in considerable increases in muscle strength. Yet despite the strong relationship between strength and locomotor function, gains in strength following strength training translate poorly into improvements in locomotor ability. By contrast, whilst task-specific training improves locomotor ability; gains are modest at best. These reviews explicitly considered the training parameters used to apply the interventions and suggested that the limited outcomes may relate to a failure to train people with stroke at sufficient intensity and dose, and with specificity to locomotor disability.

The neuroscience evidence highlighted that both spinal and cortical centres are important for the control of locomotion. Research describing neural plasticity in response to task-specific training indicated that task-specific training modifies cortical activation, resulting in long-lasting neuroplastic changes [205, 206] and that strength training modifies spinal [180, 190] and cortical excitability [190]. This theoretical evidence elucidated a role for

unilateral strength training on the affected side to act as a priming intervention to enhance corticomotor excitability prior to task-specific training in people with stroke.

The development process then involved outlining the defining features of the intervention, and explicitly stating and describing the training parameters in relation to relevance, specificity, intensity and dose. The key features of the STT intervention are that strength training is utilised to systematically prime the central nervous system prior to task-specific training. And that strength training and task-specific training are conducted in an evidence based manner to maximise gains in locomotor ability. This structured approach to intervention development addresses concerns expressed in the research literature in relation to the failure to adequately describe rehabilitation interventions [19, 20]. The external validity of the intervention was further supported consultation with key stakeholders and the development of implementation resources. This pre-clinical phase of intervention development resulted in a robust intervention grounded in the evidence which was ready for pilot testing.

Measurement of neural plasticity in response to locomotor rehabilitation

In the process of developing a study protocol designed to test the efficacy of the STT intervention in a future RCT, it became evident that a major limitation of research in this field to date was the lack of a valid and reliable measure of neural plasticity in response to locomotor rehabilitation. Therefore prior to pilot testing the intervention, two studies investigating potential outcome measures were undertaken.

The study 'Test-retest of BDNF Measures' is the first study, to the authors knowledge, to describe the reliability of BDNF measures in people with stroke and healthy participants both at rest and in response to exercise. This study also, for the first time, quantified the level of biological variability and technical error seen in measures of BDNF in humans. This study described poor to moderate reliability in this measure and modest within – subject variability. These findings contribute considerably to the growing body of research investigating BDNF in healthy [280], neurological [267] and psychiatric populations [296]; drawing a cautionary note in relation to the interpretation of studies which are likely underpowered to detect true change or difference in BDNF levels in these groups.

Given that the expected magnitude of change in BDNF in response to a rehabilitation programme in people with stroke was unknown the decision was made to utilise the measure in the pilot study to enable exploration of the likely magnitude of difference and variance estimates. The pilot study results provide preliminary evidence that the magnitude of change in response to an intensive exercise rehabilitation programme is unlikely to exceed the typical error of the measure in people with stroke. This study is also the first study to describe the increase and decrease of BDNF in response to exercise and subsequent rest in people with stroke. Whilst inferential analysis revealed no main or interaction effects between the groups, these findings should be interpreted with caution given the limited reliability of the measure.

The reliability study 'Test-retest of TMS Measures' has identified a reliable method of measuring corticomotor excitability in response to locomotor rehabilitation in people with stroke. This method also has high face validity given the task-specific nature of the neural plasticity in response to different exercise rehabilitation interventions. The assessment during a functional task represents a considerable advancement in the utilisation of TMS to measure neural plasticity in response to rehabilitation and widens the scope for investigation in people who are more severely affected following stroke. In view of the findings of both reliability studies, and the pilot trial, it was recommended that TMS-derived measures of corticomotor excitability during walking be selected as the biomarker of neural plasticity in future studies investigating the STT intervention.

Strength for Task Training: A Pilot Study

The final section of this thesis described a pilot study which sought to establish the feasibility of the study protocol of an RCT to determine the efficacy of the STT intervention. This pilot trial evaluated the acceptability, fidelity and safety of the STT intervention, and the feasibility of the research protocol using a mixed methods design. The specified criteria for the pilot study were met, and the feasibility of the study protocol was established. This included: recruiting sufficient participants within the specified timeframe, achieving greater than 95% data completeness, greater than 80% intervention adherence and fidelity, comparable rates of adverse events as previously reported for people with stroke when exercising, and that both the participants and the physiotherapist deemed the STT intervention acceptable.

The pilot study provided a comprehensive understanding of the research process, and minor amendments to the study protocol were recommended. The recruitment strategy and inclusion criteria were successful; however consideration of the most appropriate measure of cognitive impairment following stroke and the influence of cognitive impairment on the ability of the participant to engage in the rehabilitation programme is required. The requirement for data completeness was achieved, although the addition of a third assessment session and modification to the clinical documentation system is warranted. Triangulation of quantitative and qualitative data with regard to participant outcomes identified a number of omissions in the breadth of study outcome measures selected.

This research programme is one of the few to explicitly consider locomotor rehabilitation intervention acceptability as part of the intervention development process. Prior to pilot testing the intervention an extensive consultation process was undertaken with key stakeholders, this resulted in refinement of the intervention. However it is the mixed methods approach to the pilot study which has contributed most to the understanding of intervention acceptability for both participants and physiotherapists. The qualitative descriptive approach provided a rich source of data which informed the understanding of factors that promoted and challenged intervention acceptability for people with stroke. These findings emphasised the need to focus on strategies which support behaviour change and facilitate engagement in physical activity and exercise, including; strategies; which enhance self-motivation and determination, improve knowledge of the benefits of exercise, and clarify the rationale for the intervention. The explicit promotion of positive group social interactions and the individualisation of the intervention to person's specific physical issues and barriers to translation of gains to their home environment were also identified as important.

Qualitative descriptive analysis of the physiotherapists' post-intervention interviews and weekly feedback indicated that the STT intervention was highly acceptable and provided specifics related to the logistics of delivering the intervention. However greater emphasis was placed on the need to develop new ways of working to successfully implement the intervention. In particular the requirement to progress intervention based on the intensity of training and the challenges of managing group interactions were emphasised. It is important to note also that both the PRST and TST physiotherapist identified that the interventions were significantly different from their current clinical practice especially in

relation to the intensity and volume of training. To the author's knowledge, this is the first attempt in the research literature to quantify, monitor and progress the intensity of task-specific training based on a self-rated specified level of task difficulty rather than at an intensity determined by the physiotherapist. Given the importance of training intensity in driving neural plasticity, this represents an important step forward in stroke rehabilitation and is an avenue for ongoing research, which has the potential to change clinical practice.

This pilot study did not to establish precise estimates of the magnitude of the difference and variance of the outcome measures as the groups were too heterogeneous and small to provide any surety in estimation. It is important to recall that the intention of this work was to study samples which were representative of the stroke population. Whilst this promotes the external validity of the research findings it does present challenges in relation to the interpretation of results due to the heterogeneity of the respective samples.

Limitations

This body of work was predicated on the available research and theoretical knowledge base at the time of the intervention development phase. Our knowledge of neuroscience and motor control and learning, along with the rehabilitation research body of knowledge continues to grow at an exponential rate. There is a risk that the intervention could be further informed by evidence which was has been subsequently been published, although review of the recently published evidence in relation to strength training and task specific training suggest that the conclusions of the systematic reviews underpinning the intervention development remain unchanged.

Whilst both reliability studies were rigorously executed the recruitment of the participants from community sources has resulted in a limited description of the stroke samples with respect lesion location, and a sample which are in the chronic phase following stroke. The drive to ensure that the findings of this research have strong external validity has also resulted in study samples which are very heterogeneous. The research presented as part of this thesis does not consider the influence of covariates on the outcomes of interest, this is likely to be important in future work. The TMS study has described a highly reliable method of measuring neural plasticity in response to locomotor

rehabilitation; however the method requires further refinement and greater characterisation of the selection bias inherent in the measure.

A limitation of the pilot study investigating the STT intervention is that it is based on a small sample and a single cycle of the intervention conducted at a University site; this may limit the external validity of the findings. The study was not designed to draw conclusions with regard to the clinical efficacy or effectiveness of the intervention but it does make a significant contribution to the staged evaluation of the intervention as recommended by the MRC.

Conclusion

To date, in the process of development and piloting of the STT intervention, this research programme has successfully addressed a number of the criticisms of rehabilitation research described in the introduction. Specifically, this thesis has;

- facilitated the engagement of people with stroke in the intervention development process [15]
- defined the essential elements of the STT intervention and adequately described the training parameters for implementation [20, 519, 520]
- begun to explore possible mechanisms of action of the STT intervention through a mixed methods approach [18]
- compared the STT intervention to relevant parallel treatment interventions [21]
- selected outcomes which reliably measure and describe the STT intervention effect [15, 21]
- contributed to the strategic evaluation of the STT intervention in a step wise manner, by undertaking the first pilot study in a programme of research [21]

This thesis has described the development and piloting of a novel intervention to improve locomotor ability following stroke .The process has resulted in an intervention which is theoretically and evidence based, clearly defined and described, and responsive to the needs of people with stroke. The next phase in this research programme is to explore the establishment of the magnitude of difference scores and variance estimates for the

outcome measures, including measures of neural plasticity, in response to the STT intervention. It is recommended that comparison is made to an attention and dose matched standard clinical practice intervention. This next study would also enable assessment of the feasibility of conducting the intervention at a suitable community or rehabilitation site and consider the acceptability of the newly refined STT intervention.

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PUBLICATIONS AND CONFERENCE PRESENTATIONS

Signal, N. (2014). Strength training after stroke: Rationale, evidence and potential implementation barriers for physiotherapists. *New Zealand Journal of Physiotherapy*, *42*(2), 101-107.

Lewis, G. N., **Signal, N.**, & Taylor, D. (2014). Reliability of lower limb motor evoked potentials in stroke and healthy populations: how many responses are needed? *Clinical Neurophysiology*, *125*(4), 748-754. doi:10.1016/j.clinph.2013.07.029

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APPENDICES

Appendix A.   STT Intervention Manual

Strength for Task Training (STT)

An intervention to improve locomotor ability following stroke

NOTE: The physiotherapists were blinded to study hypothesis. Therefore, the training manuals provided were not titled based on the intervention.

Walking after stroke

- Stroke is the leading cause of disability in New Zealand

  Bonita et al, 1997, Tobias et al,, 2007

- Approximately 20,000 people in New Zealand have a disability as the result of stroke

- Most people who have a stroke will have difficulty walking

  Bonita et al, 1988, Dobkin et al,, 2004, Vincent et al, 2007

- Regaining walking ability is important to people following stroke

  Dobkin 2004, Vincent et al 2007, Pound 1998

- Most of time in physiotherapy is spent practicing locomotor skills

  Ballinger et al, 1999, DeWit etal 2005, Jette et al 2005, Latham et al 2005

Strength Training

The main impairment limiting locomotor function following stroke is muscle weakness.

Bohannon et al 2007, Harris et al 2001, Ng et al 2000

The relationship between strength and locomotor function is strong. It is possible to predict locomotor function from measures of strength.

Milot et al 2008, Muren et al 2008, Saunders et al 2008

Strength of specific muscles relates to specific aspects of locomotion.

For example;

Quadriceps – Sit to Stand

Plantarflexors and Hip Flexors – Walking speed

Hip Extensors – Stair climbing

Strength training following stroke improves strength, but with limited carry over to locomotor ability.

Lee 2008, Kim 2001, Flansbjer 2008

Many research studies evaluating strength training for people with stroke fail to train the participants hard enough. Clinically strength training applied in neurological populations often does not meet recommended training guidelines
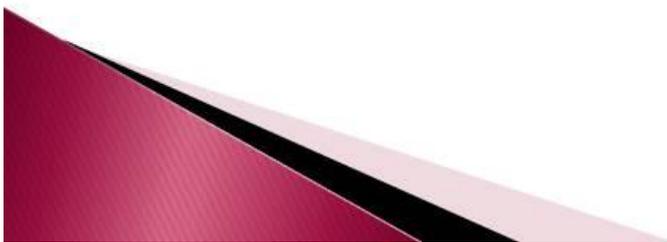
Task-specific Training

▸ Task-specific training is the repetitive practice of functional tasks, such as repeated sit-to-stand practice or repeated walking practice. This treatment is also called task specific training and task orientated training.

▸ There is evidence to support the use of task-specific training as a method of promoting motor learning and central nervous system (CNS) plasticity in both normal and stroke populations, particularly in the upper limb.

<div align="right">Stinear et al, 2008</div>

▸ A recent Cochrane review identified a paucity of high quality RCT's addressing the effects of task-specific training on locomotor function.

<div align="right">Pollock et al, 2008</div>

▸ Those studies which have investigated Task Training demonstrate that it has only a modest impact on locomotor skills.

<div align="right">McClellan 2004, Salbach 2004, Yang 2008</div>
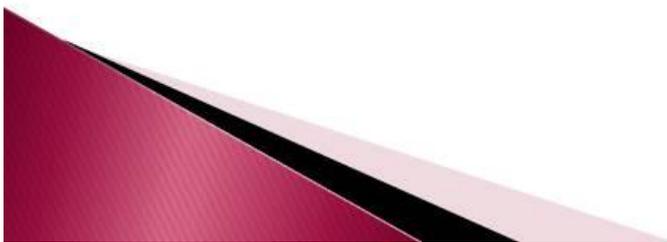
- Strength training (PRST) improves strength but not walking ability

- Practicing walking (TST) improves walking, a modest amount

So...

- How do we ensure the transfer of strength gains into locomotor function?

- How do we enhance the effect of task-specific training?

Combine the two types of training

▸ PRST *immediately followed by* TST
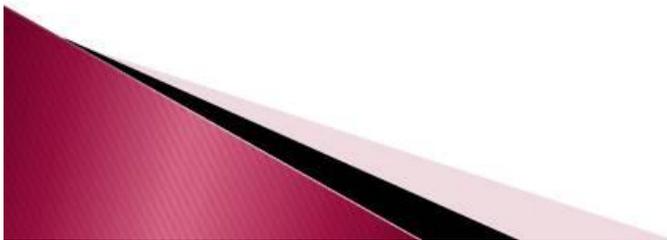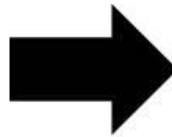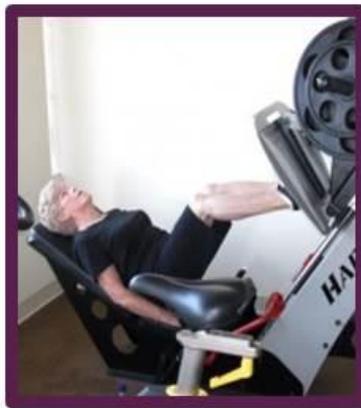
Priming

▸ Priming refers to a transitory increase in neural excitation
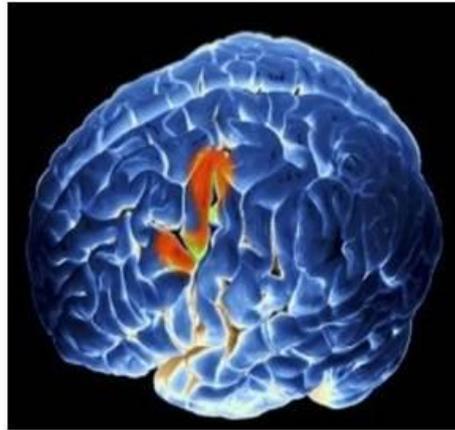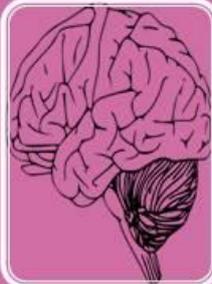
Neuroscience

- Priming with TMS, sensory input, motor imagery, movement
- Priming prior to UL task practice in stroke

Carroll et al, 2002, Adkins et al 2006, Stinear et al 2008, Woldag et al 2006
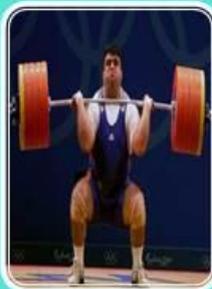
Sports Science

- (Near) Maximal effort prior to skill performance

Ebben et al, 2006 & 2000, Sale et al 2002

Athletic Training

- Combining Strength Training with sports specific training

Chimera et al, 2004, Ronnestad et al 2008, Markovic et al, 2007,

The Aim of STT

▶ Promote the transfer of strength gains into locomotor function

▶ Enhance the effect of the TST by priming the CNS prior to the task performance.

▶ Promote neural plasticity and improve motor learning.

The Programme

- Exercises: Moderate to high intensity strength training of a relevant muscle group immediately followed by repetitive practice of a locomotor skill which uses the trained muscle.
- Duration: 12 weeks
  27th June – 16th September
- Frequency: Three times per week
  Monday, Wednesday, Friday
- Intensity: Strength Training approximately 60–80% 1RM
  Task training at 'Somewhat Difficult' to 'Very Difficult'
- Volume: 1 hour per session, with very limited rest periods.
  Two minutes per exercise/task, with 30 seconds transition/rest time
- Progression: Increasing load from 60 to 80% 1RM
  Increasing task complexity across nine parameters

Station	Strength Component	Task Component
1	Seated leg press (Quadriceps)	Sit-to-stand-to-sit
2	Hamstrings (Westminster Pulley)	Walk backwards
3	Hip Extension (Westminster Pulley)	Stairs / Off Floor
4	Hip Abduction (Theraband)	Walk sideways
5	Hip Flexion (Rotary Hip)	Walk (comfortable speed)
6	Plantarflexors (Supine Leg Press)	Walk (fast speed) / Ramps
7	Dorsiflexors/Evertors (Theraband)	Obstacles

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Week 1

Getting to know participants–Introduction

Familiarisation with rooms, toilet location, Debbie the receptionist

Record participants weight, GP details and emergency contact person

Trial each exercise/task

Strength–   modest weight, aim to complete up to14 reps in a set

Task–   low complexity

Moving around gym environment and engaging with equipment

Week 2

Becoming familiar with exercise and task techniques

Follow exercise posters

Training zone education

Strength–   Increase weights to work VERY, VERY HARD by the
                 14th repetition (14-RM)

Task–   Increase task complexity gradually

Weeks 3–4

Focus on technique

Strength–   Increase weights to work VERY, VERY HARD by the
                 12th repetition (12-RM)

Task–   Increase task complexity to be working SOMEWHAT
                 DIFFCULT on each task

Weeks 5–6

Strength–   Increase weights to work VERY, VERY HARD by the
                 10th repetition (10-RM)

Task–   Increase task complexity to work at a DIFFICULT
                 intensity on each task

                 Ensure that sensory availability and attention are
                 challenged

Weeks 7–8

Strength–   Increase weights to work VERY, VERY HARD by the 8th
                 repetition (8–RM)

Task–   Maintain task complexity to work HARD on each task

                 Ensure that sensory availability and attention are
                 challenged

Weeks 9–12

Strength–   Reduce load by 20% and ask the participant to work
                 VERY, VERY HARD and VERY FAST

Task–   Increase task complexity to work VERY DIFFICULT on each
                 task

                 Ensure that environment, sensory availability and
                 attention are challenged

                 Ensure that some tasks are practiced in a random
                 fashion

Task Progression

- Task-specific training is defined by the repetitious practice of tasks. This programme has applied concepts and research from the motor control and motor learning literature.

- The fundamental aim is to;
  - Practice as many **repetitions** of each task as possible within the training session
  - Maintain an optimal level intensity of training by increasing **task complexity** to promote neural plasticity
  - Progress training to mimic **real world** locomotor skills as much as possible.

- Each task is designed to be progressed across nine parameters. The selection of which parameter is progressed, and at what rate is at the treating physiotherapists discretion.

- The images provided are to give a visual cue to the participant, please do not feel bound by them.
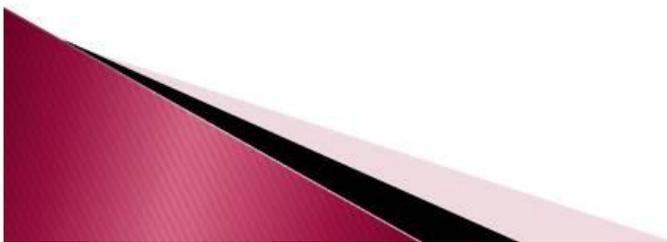
Task Progression

Often practice factors which degrade the performance of a task in the short term, improve it's learning in the long term.

Part vs. Whole

○ You can select from part-tasks which represent a component of the task being learnt (such as stepping as a component of walking) or the whole task. Part task training is a useful starting point when the whole task is too difficult for the participant or when the task represents a discrete skill. The aim should be to move toward whole task training where possible, particularly for tasks which are continuous, like walking.

Speed

○ The imposition of a speed requirement is designed to challenge the participants speed of processing, reaction and movement time, which is frequently an issue after stroke.

Accuracy

○ Requiring accuracy in a task may encourage multi-joint co-ordination. For example; stepping to a small target requires finer co-ordination than stepping to a large target.

- **Sensory Availability**
  - Sensory impairments and sensory integration for postural control are frequently an issue after stroke. Manipulation of the sensory information available during a task may force the use of the other senses i.e. reducing vision forces the use of vestibular and somatosensory information. This also mimics the real-world, as frequently not all of our sensory information is available; for example; walking whilst turning your head to talk to someone.

- **Biomechanical Challenge**
  - This parameter alters the biomechanical challenge of the task by changing things like the available Base of Support, the level of physical support and the size of the movement required.

- **Attention-Cognitive**
  - This parameter adds secondary cognitive tasks, such as doing mental arithmetic, to the primary task to promote autonomous locomotor skills and to mimic the real-world.

- **Attention- Physical**
  - This parameter adds secondary physical tasks to the primary task, again to promote autonomous locomotor skills and to mimic the real-world.

- **Environment**
  - You can change the environment in which the locomotor skill is practiced. Moving toward a more complex and variable environment is ideal.

- **Blocked vrs Random**
  - Practicing different tasks in a random order, rather than the same task repeatedly, is likely to promote motor learning once the basics of the skill have been learnt. This is also more 'real-world' i.e. getting a drink from the fridge involves moving from sit-to-stand, walking forwards, turning, stepping backwards, turning, walking forwards and then moving from stand to sit.

A word about feedback

- While some feedback is required and valuable, it is important not to over burden the participant with a lot of feedback

- Aim to:
- Reduce the amount of feedback provided over time.
- Allow the participant the opportunity to evaluate their own performance.
- Limit feedback to
  - A general summary of performance
  - Motivational feedback and encouragement
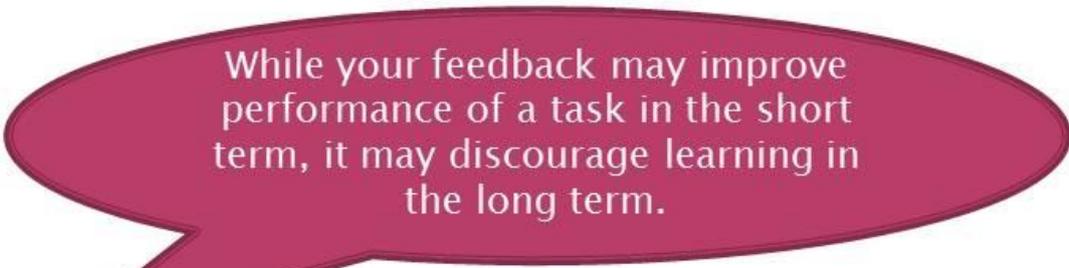
While your feedback may improve performance of a task in the short term, it may discourage learning in the long term.

Exercise and Transition Times

- The aim of the programme is that participants exercise at a moderate to high intensity for as much time as possible within the hour. There is no 'down time' scheduled; beyond the 30 second transition time between exercises.
- A short transition time between strength training and task-specific training is essential as the priming effect degrades very quickly.
- It will be important to encourage participants to transition quickly and be ready to begin the next exercise prior to the buzzer.
- An iPOD timer is set with speakers for your use.
- To use the timer:
  - Press the central key
  - Touch the arrow and slide across to unlock
  - Touch the chain timer icon (bottom left)
  - Select the Rehab to improve… programme
  - Check the volume on the iPOD and speakers are turned up to maximum
  - Touch Exercise to begin the timer
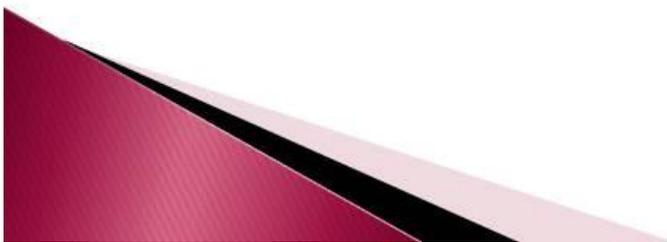
- The following are copies of the gym posters for each exercise.
- They are intended to cue the participant and to help people orientate the environment. The details of the exercise for each participant will be recorded on their intervention recording form.
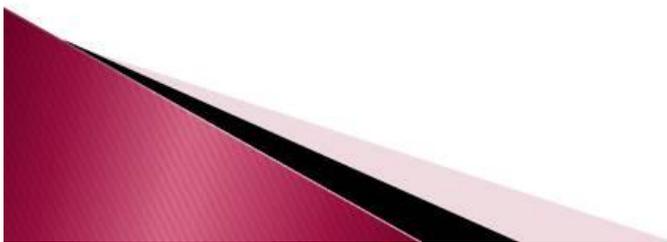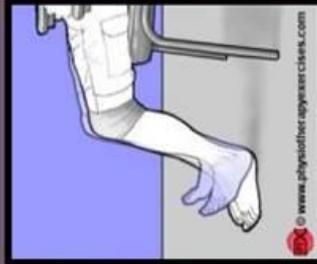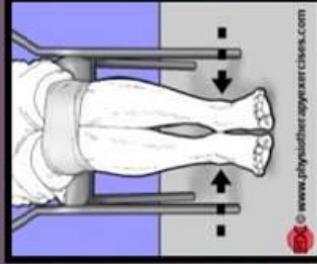
Obstacles

Navigate around obstacles

1

© www.physiotherapyexercises.com

Step over obstacles

2

© www.physiotherapyexercises.com

Step on obstacles

3

© www.physiotherapyexercises.com

FAST

Toe Ups

© www.physiotherapyexercises.com

Aim: To strengthen muscles for foot clearance

Starting Position: Seated with your knees together and feet flat on the floor

Action:
(1) Touch your ankle bones together, hold and then...
(2) Pull your toes up, hold

Progressions: Theraband

Modifications: Move feet forward of knees *or* Position on sloped step to increase Range of Motion
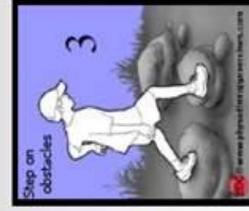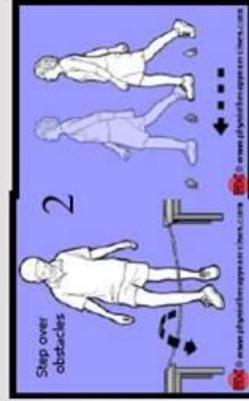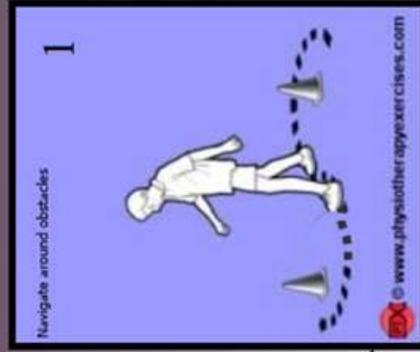
Hip Flexors
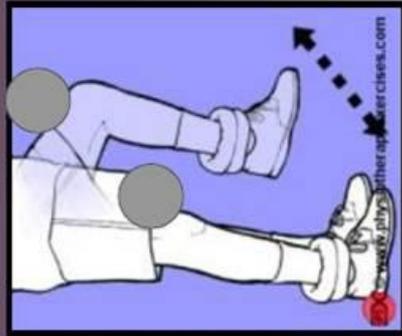
Aim: To strengthen muscles at the front of the hip

Starting Position: Stand in the Rotary hip machine with your affected leg inner most. Position the pad against your upper thigh. Hold the handle n front.

Action: Bring your knee forward and upward.

Progressions: Increase weight
Begin with foot behind stance leg

FAST

Walking & Stepping

Forwards walking

1

Forwards stepping

2

Multi-tasking

3

Walking on a line

4

Hip Abduction

Sideways Walking & Stepping
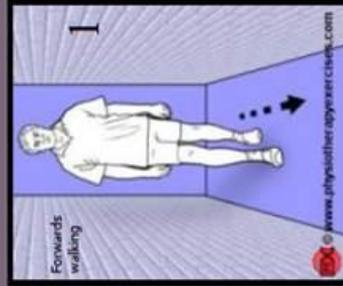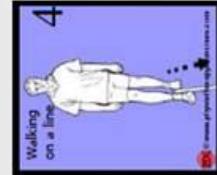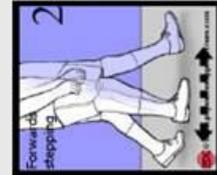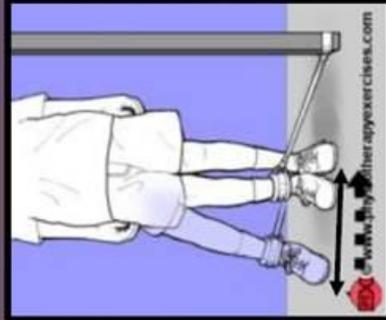
Aim: To strengthen muscles at the side of the hip muscles

Starting Position: Attach the ankle cuff to your affected leg. Stand side-on to the Theraband with your hands resting on plinth

Action: Move your leg away from the midline

Progressions: Theraband

Modifications: Raise plinth and support body weight through elbows
Complete in Supine position

FAST

Standing Up & Sitting Down
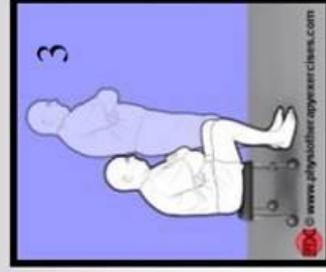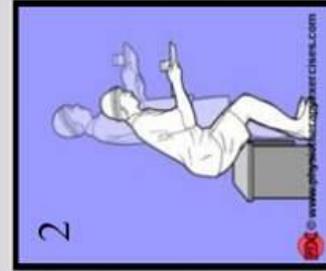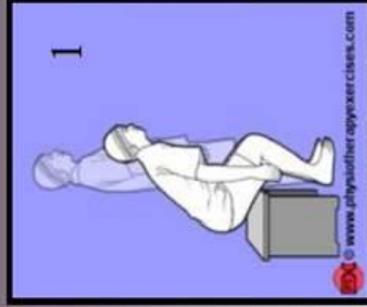
FAST
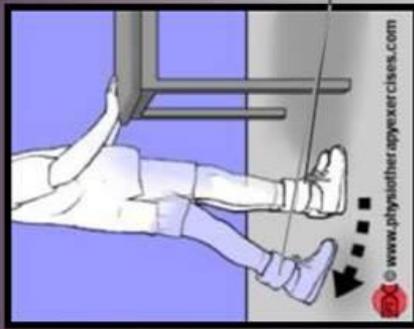
Leg Press

Aim: To strengthen quadriceps muscle at the front of the thigh

Starting Position: Sitting in the Leg Press machine with affected foot on foot plate.

Action: Push through your foot to straighten your knee.

Progressions: Increase weight

Modifications: Use two feet

Stairs & Steps

Stairs — 1

Steps — 2

Step Ladder — 3

Up from Floor — 4

© www.physiotherapyexercises.com

FAST

Hip Extension

© www.physiotherapyexercises.com

Aim: To strengthen buttock muscles

Starting Position: Attach the ankle cuff to your affected leg. Stand facing the pulley system with your hands resting on plinth/bed

Action: Move your leg backwards, keeping your knee straight

Progressions: Increase weight

Modifications: Raise plinth and support body weight through elbows

Backwards Walking & Stepping

Backwards walking — 1

Backwards stepping — 2

Backwards Step & Pivot — 3
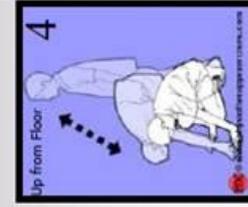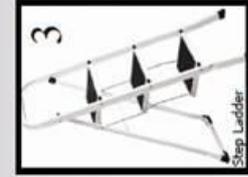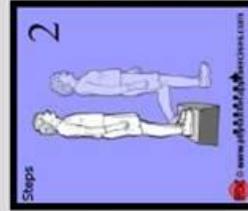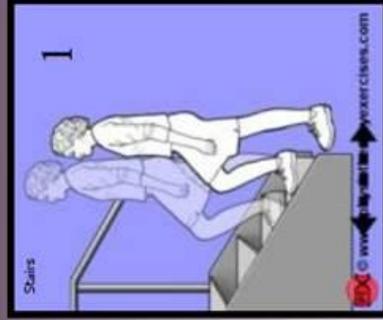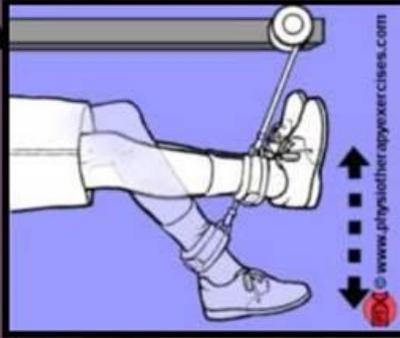
FAST

Hamstrings

Aim: To strengthen hamstring muscles at the back of the thigh

Starting Position: Attach the ankle cuff to your affected leg. Stand facing the pulley system with your hands resting on plinth/bed

Action: Keeping your hip still, bend your knee.

Progressions: Increase weight

Modifications: Raise plinth and support body weight through elbows

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Heel Raise   Fast Walking & Slopes

FAST

Aim: To strengthen calf muscles

Starting Position: Lying on your back in the Leg Press with your affected foot flat on the foot plate.

Action: Push through your toes to raise your heel

Progressions: Increase weight

Modifications: Complete with two feet

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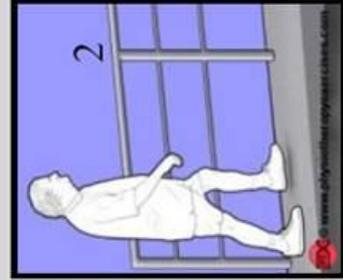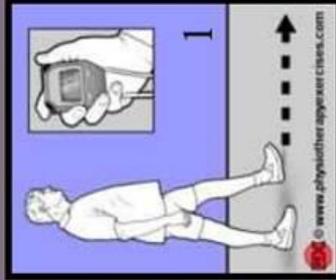
- The next section provides some details for ensuring specificity of training in the strength training component. The intent is to mimic the action of the muscle in the task as closely as possible.

Exercises: Plantar Flexors

Heel Raise

Provide 1–3 pillows for head and neck support
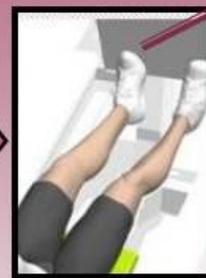
Use only the affected leg on the foot plate. The other leg can rest on the side or be secured with a seat belt. If the participant is unable to stabilize their affected foot on the footplate use the strap provided

Take extra care when getting on and off the machine as there is lots of metal bits. Hold the trolley still if necessary. Have the participant sit side on, place their legs in, swivel around and then lie down

Aim: To strengthen calf muscles

Starting Position: Lying on your back in the Leg Press with your affected foot flat on the foot plate.

Action: Push through your toes to raise your heel

Progressions: Increase weight

Modifications: Complete with two feet

The aim is to recruit both soleus and gastrocnemius, so the knee should be in a semiextended position. Begin in as much dorsiflexion as possible

Exercises: Hip Flexors

Hip Flexors
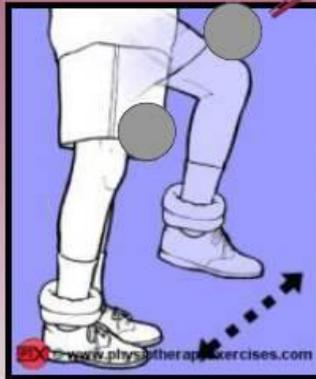
Check the pad position in full flexion

This machine requires some demonstration

Aim: To strengthen hip muscles

Starting Position: Stand in the Rotary hip machine with your affected leg inner most. Position the pad against your mid-thigh. Hold the handle in front.

Action: Bring your knee forward and upward.

Progressions: Increase weight
Begin in hip extension

Modifications:

The hip flexors are important in the outer part of the range (15° extension to 0°) so the sooner training from an extended position begins the better

Exercises: Hip Abductors

Hip Abductio[n]

Stabilise with hands on a plinth or table
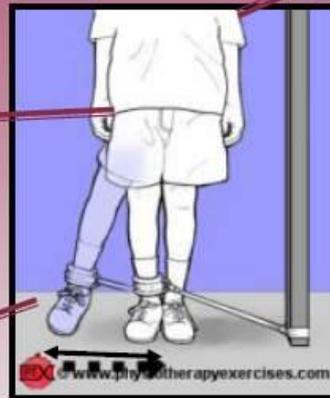
Watch for neutral pelvic and trunk position through out

Check that foot faces forwards

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Aim:	To strengthen hip muscles
Starting Position:	Attach the ankle cuff to your affected leg. Stand side-on to the Theraband with your hands resting on the plinth/bed.
Action:	Move your leg away from the midline
Progressions:	Theraband
Modifications:	Raise plinth and support body weight through elbows Complete in Supine position

This is the actual order of progression for the Theraband

Exercises: Quadriceps

Leg Press

Check not recruiting plantar flexors
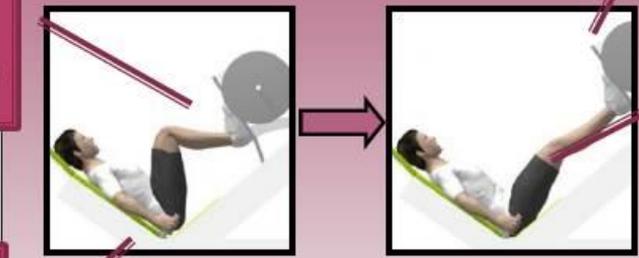
Monitor knee and hip position

Use only the affected leg on the foot plate. The other leg can rest on the side or be secured with a seat belt. If the participant is unable to stabilize their foot on the footplate use the strap provided

Alter the seat position to start from as much hip and knee flexion as possible.

Aim: To strengthen quadriceps muscle

Starting Position: Sitting in the Leg Press machine with affected foot on foot plate.

Action: Push through your foot to straighten your knee.

Progressions: Increase weight

Modifications: Use two feet

Exercises: Evertors & Dorsiflexors

Toe Ups

Secure the knees only if the participant can not hold them together

Altering the position of the feet relative to the knees (forward or back) will change the RoM that the person can move through. It maybe easier to start with the feet further forward

Aim: To strengthen muscles for foot clearance

Starting Position: Seated with your knees together and feet flat on the floor

Action:
(1) Touch your ankle bones together, hold and then...
(2) Pull your toes up, hold

Progressions: Theraband

Modifications: Move feet forward of knees *or* Position on sloped step to increase RoM

(1) To recruit evertors initially draw medial malleoli together and lift lateral border of feet

(2) Then recruit dorsiflexors

(3) Progress to a unilateral action as soon as possible

Secure the Theraband around a low box step. This is the actual order of progression for the Theraband

Exercises: Hip Extensors

Hip Extension
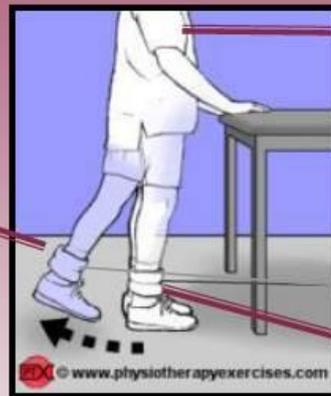
Monitor trunk, hip and knee position. Discourage trunk and knee flexion

Encourage the participant to work into full extension

Begin the movement from a hip flexed position

© www.physiotherapyexercises.com

Aim:	To strengthen buttock muscles
Starting Position:	Attach the ankle cuff to your affected leg. Stand facing the pulley system with your hands resting on the plinth/bed
Action:	Move your leg backwards, keeping your knee straight
Progressions:	Increase weight
Modifications:	Raise plinth and support body weight through elbows

Exercises: Hamstrings

Hamstrings

Monitor trunk and hip position. Discourage trunk and hip flexion

Encourage the participant to work into full flexion

© www.physiotherapyexercises.com

Aim:	To strengthen hamstring muscles
Starting Position:	Attach the ankle cuff to your affected leg. Stand facing the pulley system with your hands resting on plinth/bed
Action:	Keeping your hip still, bend your knee.
Progressions:	Increase weight
Modifications:	Raise plinth and support body weight through elbows

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Managing Risks

▸ **Research Team**

▸ Participants enrolled in this study have been screened for relevant contraindications and cautions to high intensity rehabilitation (i.e. cardiac conditions, metabolic conditions, uncontrolled hypertension, significant arthritis and/or musculoskeletal pain) by a registered physiotherapist prior to inclusion in the study

▸ In addition, each participant's General Practitioner or other nominated medical specialist has been notified of their intended participation in the study and asked to contact the research team if they have any concerns about their patient's participation.

▸ This study has ethical approval from the Northern Regional Ethics committee.

▸ **Physiotherapists**

▸ As a New Zealand registered physiotherapist you are required to meet your obligations under the Health Practitioners Competence Assurance Act, the NZ Board of Physiotherapy Standards of Ethical Conduct, the Privacy Act and the Code of Consumer Rights (Health and Disability Commissioner Act).

▸ Each participants biography outlines any cautions which have been identified in relation to high intensity rehabilitation, along with the results of their physical assessment. This information should help you to manage any risks associated with rehabilitation for that particular participant. Please also refer to the section on reporting 'Adverse Events' and 'Monitoring participant response to rehabilitation' below.

▸ **Adverse Events**

▸ An adverse event is defined as an event that causes the participant to seek attention from a health professional, or limits their activities of daily living for at least two days. All adverse events should be immediately reported by telephone to Liz Binns or Nicola Towersey and the attached documentation completed. Serious adverse events will be reported to the funding body and ethics committee.

▸ If there is any indication that the research is harmful for participants, it will be stopped and the situation reviewed (including consultation with relevant parties or bodies) before making a decision about whether to continue.

Emergency Protocols

▶ **Emergencies**
  ◦ In the event of an emergency **dial 1 for an outside line.** Then **dial 111 for emergency services.**
  ◦ State the emergency service you need: fire, police or ambulance
  ◦ Tell the emergency operator the address for service:

          AUT University– Akoranga Campus
          90 Akoranga Drive
          Northcote.
          Gate 2
          Carpark 5
          Occupation and Rehabilitation studies
          Room AA111

  ◦ Give the emergency operator your phone number and extension number
  ◦ Send someone to the entrance of Gate 2 to direct emergency staff
  ◦ You should also notify AUT Security on extension 9997
  ◦ Do not hesitate to yell for help and bang on the doors of the adjacent offices and research laboratories
  ◦ You will find a **first aid kit, oxygen and a cardiac defibrillator** on the kitchen bench in the lab.

▶ **Medical Support**
  ◦ Medical support for heath issues which are **not** emergencies can be provided by AUT Health and Counselling Services. You can request their assistance by dialling ext 8888.
  ◦ You will find the GP name and emergency contact person details for each participant on their biography.
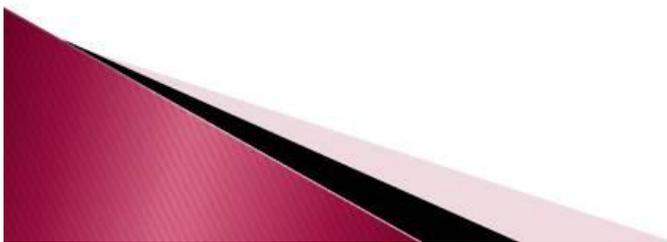
Adverse Event Reporting

An Adverse Event is any event related or unrelated to the rehabilitation intervention which causes the participant to seek attention from a health professional, or limits their activities of daily living for at least two days.

Adverse Event Reporting Form

An adverse event is defined as an event that causes the participant to seek attention from a health professional, or limits their activities of daily living for at least two days.

If such an event should occur, please report this by emailing the form below to liz.binns@aut.ac.nz as soon as possible. Please also discuss the event with either Liz Binns or Nicola Towersey as soon as possible.

Participant Details:
Patient's full name: Sex: Male Female

Date of birth: /   /   GP Name and contact details:

Treating physiotherapist: :

AE Description:
Date event occurred: /   /
Outcome: Fatal   Recovered   Continuing

Details of adverse event:
_____
_____
_____
_____
_____
_____

Did the event require medical care or hospitalisation?   No Yes
Details of care required:
_____
_____
_____

Reason why you consider event to be related to the rehabilitation programme:
_____
_____
_____

Name of person reporting:

Telephone Number:

Monitoring participant response to rehabilitation

- As the treating physiotherapist you will monitor individual and group response to the intervention at each contact with the participants. In addition to recording session content and response for individual participants, please provide a weekly report to the research team outlining any issues, concerns and general impressions of the rehabilitation sessions.

- Individual participant response to the rehabilitation is monitored using Rating of Perceived Exertion and Task Difficulty, subjective feedback from participants and your observation of the participant before, during and after the class. In addition a pulse oximeter and sphygmomanometer are available from George Palmer telephone 921 9005.

- Participants may find the rehabilitation programme physically demanding and may experience the fatigue and physical discomfort that is sometimes associated with starting a new exercise regime. This risk is minimised as the exercise intensity is gradually increased over the first two weeks of familiarisation and determined based on the individuals' abilities and fitness. It is important to closely monitor exertion levels and technique during the rehabilitation.

- Please be aware that if you have concerns for a participants safety or wellbeing you are able to terminate the rehabilitation session. The participants are also able to terminate a rehabilitation session at any stage. Please contact Liz Binns 921 9785 or Nicola Towersey 921 9999 ext. 7641 to discuss any issues.

- Adverse Events are to be recorded in writing and Liz Binns or Nicola Towersey notified immediately. Please see above for more information.
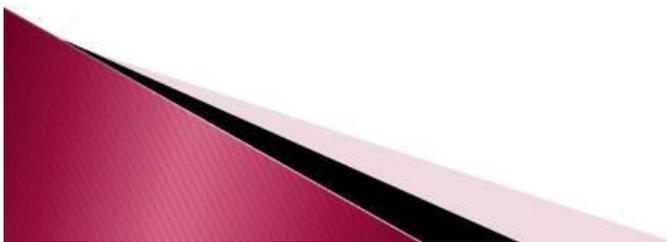
Planning & Documentation

- ▸ **Recording Information for the study**
- ▸ You will receive a memory stick which has electronic versions of all relevant forms saved on it. These include;
  - ▪ Participant Biographies
  - ▪ Participant intervention planning and documentation Master Form
  - ▪ Adverse Event Reporting Form
  - ▪ Weekly Feedback Form
- ▸ At the end of the study you will have saved to the memory stick;
  - ▪ A copy of each participants intervention planning and recording sheet for each session. i.e. 36 separate documents.
  - ▪ A copy of any adverse event forms
  - ▪ A copy of each weekly feedback form i.e. 12 separate documents
- ▸ **Individual Participant Planning and Documentation**
- ▸ The Participant intervention planning and recording Excel spreadsheet is labelled using the participants initials and the date of the first session.
- ▸ The first session settings are already selected, this session is designed to provide a very light workload and enable you to get to know the participants and the exercises.
- ▸ You should print off a copy of each participants planned programme *before* the session. Use this to guide the programme and record any changes and comments on it in pen.
- ▸ As soon as able after the session, electronically update the participants intervention planning and recording sheet to record what *actually occurred during the session*, save this using the participants initials and the date as the file name.
- ▸ Then plan the next session for the participant and print.

Individual Participant Planning and Documentation

Below is a screen shot of the Intervention Planning and Documentation form as it should appear on your computer. To record the intervention of each participant:

1. Check the name is correct
2. Update the date of the session
3. Check the parameters for each task are correct (Columns D-L)
4. Record the number of Task Sets completed (Column M)
5. Record the weight and number of exercise sets completed for strength training
6. Record the Rating of Perceived Exertion for each exercise and task (Column C).
7. Document any exercise/task specific comments (Column N).
8. Document any general comments (Cell B25).
9. Click File- Save As
10. Change the file name to the participants initials and the date of the session.
11. Save

To select from the available parameters in a cell Click on the cell to see the drop down box arrow

By clicking on the arrow the drop down box will appear. Select the parameter required by scrolling down with your mouse and clicking.

Programme Review

If effective this programme may form the basis of an intervention which is recommended for clinical practice. We value your feedback about the programme to facilitate its development. Please complete the form below and email to Liz Binns each week.

Weekly Review of Rehabilitation Programme

Group: A   B   C   (please circle)

Date:

Physiotherapist: _____

Please provide comment on the positives and challenges of the following:

Logistics	
Environment & Equipment	
Group Dynamics	
Participant response to programme	
Exercises	

Any other comments, feedback or concerns:
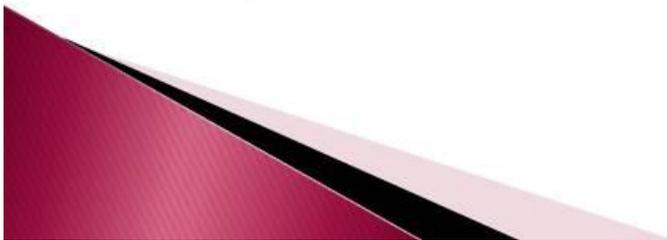
Maintaining Research Integrity

- A fundamental aspect of any randomised clinical trial is the maintenance of blinding. All of the research team, other than Liz Binns and Nicola Towersey, are blinded to which group each participant has been allocated. In order to maintain this blinding it is important not to discuss the specifics of any participant with members of the research team other than Liz Binns or Nicola Towersey. If you have any concerns about a participant please contact Liz and Nicola.

- The participants, physiotherapists and physiotherapy assistants are blinded to the hypothesis of the study. They will only be aware of the content of the rehabilitation intervention which they are participating in. Please do not discuss the specifics of the intervention or your ideas about it's likely effectiveness with anyone (including other staff or members of the research team) during the course of the research. If you have any concerns about the rehabilitation programme please contact Liz and Nicola.

Staffing & Contacts

▸ **Room Access**
  ◦ Keys to AA111 hang in the Post-Graduate Room. The code for this room is C0

▸ **Programme or Participant Queries**
  ◦ Liz Binns or Nicola Towersey
  ◦ Phone 921 9785
  ◦ Nicola's mobile 021 1292679
  ◦ Email liz.binns@aut.ac.nz or nicola.towersey@aut.ac.nz

▸ **Transport or Participant Liaison**
  ◦ Debbie Holden
  ◦ Phone 921 9999 ext. 7705
  ◦ Email debbie.holden@aut.ac.nz

▸ **Equipment or Room Issues**
  ◦ George Palmer
  ◦ Phone 921 9005
  ◦ Email george.palmer@aut.ac.nz

▸ **Security**
  ◦ Ext. 9997

Appendix B. BDNF Study - Ethics Approval

AUT
UNIVERSITY
TE WĀNANGA ARONUI O TĀMAKI MAKAU RAU

MEMORANDUM
Auckland University of Technology Ethics Committee (AUTEC)

To:	Denise Taylor
From:	**Madeline Banda** Executive Secretary, AUTEC
Date:	23 October 2009
Subject:	Ethics Application Number 09/229 **The reliability of blood serum derived measures of brain derived neurotrophic factor in healthy participants and participants with chronic stroke.**

Dear Denise

I am pleased to advise that the Auckland University of Technology Ethics Committee (AUTEC) approved your ethics application at their meeting on 12 October 2009, subject to the following conditions:

1. Inclusion of the required statement in the footer of the Information Sheets as given in the Information Sheet exemplar in the Ethics Knowledge Base (accessible online via http://www.aut.ac.nz/research/research-ethics);

2. Inclusion of the AUT logo in the newspaper advertisement.

I request that you provide the Ethics Coordinator with a written response to the points raised in these conditions at your earliest convenience, indicating either how you have satisfied these points or proposing an alternative approach. AUTEC also requires written evidence of any altered documents, such as Information Sheets, surveys etc. Once this response and its supporting written evidence has been received and confirmed as satisfying the Committee's points, you will be notified of the full approval of your ethics application.

When approval has been given subject to conditions, full approval is not effective until *all* the concerns expressed in the conditions have been met to the satisfaction of the Committee. Data collection may not commence until full approval has been confirmed. Should these conditions not be satisfactorily met within six months, your application may be closed and you will need to submit a new application should you wish to continue with this research project.

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

Yours sincerely

Madeline Banda
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: Nada Signal nada.signal@aut.ac.nz, Kathryn McPherson

From the desk of …	Private Bag 92006, Auckland 1142	Tel: 64 9 921 9999
Madeline Banda	New Zealand	ext 8044
Executive Secretary	E-mail: ethics@aut.ac.nz	Fax: 64 9 921 9925
AUTEC		page 1 of 1

Appendix C. BDNF Study Information Sheet

Participant Information Sheet

AUT UNIVERSITY
TE WĀNANGA ARONUI O TĀMAKI MAKAU RAU

Date Information Sheet Produced:

28th September 2009

Project Title

The reliability of blood serum derived measures of brain derived neurotrophic factor in healthy participants and participants with chronic stroke

An Invitation

The Researchers:

Nada Signal, Lecturer, Senior Research Officer and Doctoral Candidate, Health and Rehabilitation Research Centre, AUT University

Denise Taylor, Associate Professor, Health and Rehabilitation Research Centre, AUT University

We invite you to participate in our study to determine the reliability of blood serum derived measures of brain derived neurotrophic factor.

What is the purpose of this research?

The aim of the project is to determine if a substance in the blood (BDNF) can be reliably measured. BDNF (brain derived neurotrophic factor) is found in the brain and in the circulating blood. BDNF is an important substance that helps to protect neurons (brain cells) from damage and is thought to play a role in the recovery of movement following a stroke. There is some research that suggests exercise causes an increase in the amount of BDNF in the circulation. We want to see if a sub-maximal bout of exercise can be used to increase BDNF levels. Before we do this we need to see if it can be reliably measured. In this project we will be able to determine if BDNF can be reliably measured and if it is increased with a bout of exercise.

As part of the project we will also measure blood lactate levels, this will help us to determine how hard you were exercising by providing a physiological indication of exercise intensity.

If the results of this project indicate that BDNF is a reliable measure in people with stroke we will use it in future research projects looking at the effect of exercise based rehabilitation on recovery of function in people with stroke.

How was I chosen for this invitation?

Participation in this study is voluntary. We are looking for volunteers who either; have sustained a stroke and have some difficulty with walking, or are age matched healthy individuals.

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What will happen in this research?

Two identical testing sessions will be held 7-14 days apart. On arrival in the Exercise Laboratory participants will rest for 30 minutes in a seated position. The purpose of the rest period is to ensure that a resting heart rate is attained and that any exertion from walking to the laboratory does not affect the measures. Prior to starting exercise a cannula (type of needle) will be inserted into either the hand or elbow depending on the suitability of the participants veins (this decision will be made by the phlebotomist in consultation with the participant at the time). A baseline blood sample will be taken (5ml). Then the participant will exercise at a moderate intensity for 20 minutes on an exercycle (stationary bike). Following the exercise participants will be seated in a comfortable chair and asked to rest for a further 30 minutes.

Blood samples will be taken 10 minutes into the exercise, immediately following the exercise and 10, 20 and 30 minutes post exercise (6 blood samples drawn from each participant).

There will be two sessions held seven to fourteen days apart. Each testing session will last about an hour and a half.

What are the discomforts and risks?

Blood: the process of cannulation (needle insertion) may be mildly uncomfortable for participants. This is not unlike having your blood taken for a routine blood test.

Exercise: the sub-maximal exercise may be physically demanding for participants who don't exercise on a regular basis.

How will these discomforts and risks be alleviated?

Blood: An experienced phlebotomist who is certified in venous cannulation will be taking the blood samples, this will help to minimise discomfort.

Exercise: As the exercise intensity is determined by the participant (from the Borg scale of perceived exertion) this is likely to be a minimal risk.

Participants are able to terminate an experimental session at any stage.

What are the benefits?

There are no immediate benefits for participants. However the results of this study may be used to develop a wider clinical trial aimed at improving walking ability in people following stroke.

What compensation is available for injury or negligence?

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

How will my privacy be protected?

All participants' results will be identified by a code number only. Researchers will only have access to coded data, which will exclude their knowing the identity of any participant. Consent forms are locked away in a separate location from the data, so no association can be made between the results and the consent forms. All results are pooled, so no names of participants or any material that could identify an individual will be published or presented.

What are the costs of participating in this research?

The cost will be your time. Reimbursement towards travel expenses will be provided.

What opportunity do I have to consider this invitation?

This study will begin in November 2009. When you contact us, you will be given a verbal explanation of the study and any questions you have will be answered. An appointment to attend will be made at least one week away, so you have a further week to consider whether you wish to take part. You will be contacted after that week to confirm whether you wish to participate.

How do I agree to participate in this research?

Contact Nada Signal 921 9999 ext 7062 to arrange a time to attend or to discuss the trial further.

Before participating, you will be given a consent form to read and sign. You may withdraw from the study at any time without being disadvantaged and no reason needs to be given for withdrawing from the study.

Will I receive feedback on the results of this research?

Yes. You will be asked if you wish to receive a brief summary of the results of the project once data collection and analyses is completed. Results will be sent to all participants who indicate that they wish to receive it. The information will not identify individual results but will be a summary of the group results.

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

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisor, Denise Taylor ph 921 9680 or denise.taylor@aut.ac.nz.

Concerns regarding the conduct of the research should be notified to the Executive Secretary, AUTEC, Madeline Banda, *madeline.banda@aut.ac.nz* , 921 9999 ext 8044.

Whom do I contact for further information about this research?

Researcher Contact Details:

You can contact the research team if you want further information.

Nada Signal   921 9999 ext 7062 /email nada.signal@aut.ac.nz

Denise Taylor 921 9680 /email denise.taylor@aut.ac.nz

Approved by the Auckland University of Technology Ethics Committee on 12 October 2009, AUTEC Reference number 09/229.

Appendix D. BDNF Study Consent Form

Consent Form

AUT
UNIVERSITY
TE WÄNANGA ARONUI O TAMAKI MAKAU RAU

Project title: The reliability of blood serum derived measures of brain derived neurotrophic factor in healthy participants and participants with chronic stroke

Project Supervisor: **Denise Taylor**

Researcher: **Nada Signal**

- ○ I have read and understood the information provided about this research project in the Information Sheet dated September 2009.
- ○ I have had an opportunity to ask questions and to have them answered.
- ○ I understand that I may withdraw myself or any information that I have provided for this project at any time prior to completion of data collection, without being disadvantaged in any way.
- ○ I am aware that I may be excluded from participation in the study for any of the following reasons:
    - a) Unstable heart condition
    - b) Brainstem or cerebellar stroke
    - c) Unable to walk 10m with or without a walking device
    - d) Co-morbidities that would detrimentally affect the person's ability to participate in a cycle exercise task
    - e) In the stroke group, if the GP has not given medical clearance to participate in low-moderate level exercise.
    - f) Fear of needles.
    - g) Received a blood product or blood transfusion within the 4 weeks prior to the study commencing
    - h) Taking medications which adversely effect blood coagulation, such as Warfarin.

○　　I agree to take part in this research.
○　　I wish to receive a copy of the report from the research (please tick one): YesO　NoO
○　　I wish to be contacted about the possibility of participating in future studies undertaken
　　　by the neurophysiology laboratory of the Health and Rehabilitation Research Centre of
　　　AUT University (please tick one): YesO　NoO

Participant's signature:...

Participant's name...

Participant's Contact Details (if appropriate):

....

....

....

Date:

Approved by the Auckland University of Technology Ethics Committee on 3/11/2009
AUTEC Reference number 09/229

Note: The Participant should retain a copy of this form

Appendix E.   TMS Study – Ethics Approval

AUT
UNIVERSITY

MEMORANDUM
Auckland University of Technology Ethics Committee (AUTEC)

To:	Denise Taylor
From:	**Madeline Banda** Executive Secretary, AUTEC
Date:	26 June 2009
Subject:	Ethics Application Number 09/128 **The reliability of Transcranial Magnetic Stimulation derived measures of cortical excitability during walking in healthy subjects and people with stroke.**

Dear Denise

I am pleased to advise that the Auckland University of Technology Ethics Committee (AUTEC) approved your ethics application at their meeting on 15 June 2009, subject to the following conditions:

1. Inclusion of the AUT logo in the advertisements;

2. Inclusion of the exclusion criteria given in the response to section D.1.3 of the application in a bullet point in the Consent Form;

3. Amendment of the Information Sheet as follows:

    a. Clearer identification in either the section titled 'An Invitation' or that titled 'What is the purpose...' that this study forms part of a PhD;

    b. Alteration of the first sentence in the second paragraph of the section titled 'What are the discomforts...' to read something like 'The magnetic Simulation machine being used is not recommended for use with people who have ...';

    c. Use of the required wording for the section titled 'What compensation...' as given in the Information Sheet exemplar in the Ethics Knowledge Base (accessible online via http://www.aut.ac.nz/research/research-ethics);

    d. Alteration of the second sentence in the section titled 'What are the costs...' to read something like 'Reimbursement towards travel expenses will be provided'.

AUTEC commends the applicant and researcher on the quality of their application.

I request that you provide the Ethics Coordinator with a written response to the points raised in these conditions at your earliest convenience, indicating either how you have satisfied these points or proposing an alternative approach. AUTEC also requires written evidence of any altered documents, such as Information Sheets, surveys etc. Once this response and its supporting written evidence has been received and confirmed as satisfying the Committee's points, you will be notified of the full approval of your ethics application.

When approval has been given subject to conditions, full approval is not effective until all the concerns expressed in the conditions have been met to the satisfaction of the Committee. Data collection may not commence until full approval has been confirmed. Should these conditions not be satisfactorily met within six months, your application may be closed and you will need to submit a new application should you wish to continue with this research project.

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

Yours sincerely

Madeline Banda
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: Nada Signal nada.signal@aut.ac.nz, Gwyn Lewis, Kathryn McPherson

Appendix F.   TMS Study Information Sheet

Participant Information Sheet

AUT
UNIVERSITY
TE WĀNANGA ARONUI O TAMAKI MAKAU RAU

Date Information Sheet Produced:

6 April 2009

Project Title

The reliability of Transcranial Magnetic Stimulation (TMS) derived measures of cortical excitability during walking in healthy subjects and people with stroke

An Invitation

The Researchers:

Nada Signal, Lecturer, Senior Research Officer and Doctoral Candidate, Health and Rehabilitation Research Centre, AUT University

Gwyn Lewis, Post Doctoral Researcher and Senior Lecturer, Health and Rehabilitation Research Centre, AUT University

Denise Taylor, Associate Professor, Health and Rehabilitation Research Centre, AUT University

We invite you to participate in our study to determine the reliability of TMS derived measures of cortical excitability during walking.

What is the purpose of this research?

Research investigating how the brain controls movement is increasingly drawing on Transcranial Magnetic Stimulation (TMS) measures obtained during movement tasks. TMS measures obtained during movement can tell us not only how the brain works to control movement but, how it controls movement after the brain is damaged by stroke. The aim of this research is to develop these new techniques and to ensure that they are reliable methods of measuring brain activity during walking in healthy adults and people with stroke.

This knowledge is likely to aid in the development and evaluation of future rehabilitation interventions aimed at improving walking in people with stroke.

This study forms part of Nada Signal's research for her Doctorate of Philosophy and the results of this work will be published as part of her thesis, through conference presentations and in research journals.

How was I chosen for this invitation?

Participation in this study is voluntary. We are looking for volunteers who either; have sustained a stroke and have some difficulty with walking, or are age matched healthy individuals.

What will happen in this research?

Adhesive electrodes are placed onto the skin of the leg, for recording muscle activity. Using a *Magnetic Stimulator machine,* the researcher delivers small magnetic pulses onto participant's scalp. These pulses activate the nerve cells in the brain, which results in a small twitch in the leg muscles. The electrodes on the leg record this muscle activity. These measurements will be conducted at low levels of muscle contraction in sitting and during walking. This procedure is completely painless.

There will be two sessions held seven days apart. Each testing sesson will last about two and a half hours.

What are the discomforts and risks?

The *magnetic stimulator* is completely painless, but does cause the muscles in the leg and sometimes in the face to twitch. This carries no risk. Also, some people find the 'click' noise associated with the magnetic stimulation annoying.

The Magnetic Simulation machine is not recommended for use in people who have epilepsy, pacemakers, or metal skull, facial or jaw implants. Metal fillings in teeth are not an exclusion criteria. Therefore, volunteers who have epilepsy, pacemakers or metal skull implants will be excluded from the study.

Small areas of skin on the leg need to be shaved, and wiped with alcohol before the adhesive electrodes can be attached. This can cause a temporary stinging sensation and may cause minor, transient skin reddening.

Treadmill walking is a potentially physically demanding activity for people with stroke. In addition, there is a small risk of tripping on the treadmill.

How will these discomforts and risks be alleviated?

Participants are able to terminate an experimental session at any stage.

Strict adherence to the exclusion criteria will minimise any risk of seizure during the use of TMS. The intensity of the magnetic stimulator will begin at a very low level, allowing participants time to get used to the muscle twitch sensation. Ear plugs will be offered to reduce the noise of the stimulation and stimulation will be terminated if the participant reports any discomfort.

To minimise skin reddening from the electrodes, hypoallergenic tape is used to secure electrodes and aloe vera cream will be available in the laboratory for participants.

During treadmill walking participants will walk at their comfortable pace and will be offered regular rests. Participants will hold onto a safety rail and be attached to an overhead safety system via a body harness to prevent trips or falls.

What are the benefits?

There are no immediate benefits for participants. However the results of this study may be used to develop a wider clinical trial aimed at improving walking ability in people following stroke.

What compensation is available for injury or negligence?

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

How will my privacy be protected?

All participants' results will be identified by a code number only. Researchers will only have access to coded data, which will exclude their knowing the identity of any participant. Consent forms are locked away in a separate location from the data, so no association can be made between the results and the consent forms. All results are pooled, so no names of participants or any material that could identify an individual will be published or presented.

What are the costs of participating in this research?

The cost will be your time. Reimbursement towards travel expenses will be provided.

What opportunity do I have to consider this invitation?

This study will begin in August 2009. When you contact us, you will be given a verbal explanation of the study and any questions you have will be answered. An appointment to attend will be made at least one week away, so you have a further week to consider whether you wish to take part. You will be contacted after that week to confirm whether you wish to participate.

How do I agree to participate in this research?

Contact Nada Signal 921 9999 ext 7062 to arrange a time to attend or to discuss the trial further.

Before participating, you will be given a consent form to read and sign. You may withdraw from the study at any time without being disadvantaged and no reason needs to be given for withdrawing from the study.

Will I receive feedback on the results of this research?

Yes. You will be asked if you wish to receive a brief summary of the results of the project once data collection and analyses is completed. Results will be sent to all participants who indicate that they wish to receive it. The information will not identify individual results but will be a summary of the group results.

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

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisor, Denise Taylor ph 921 9999 or denise.taylor@aut.ac.nz.

Concerns regarding the conduct of the research should be notified to the Executive Secretary, AUTEC, Madeline Banda, *madeline.banda@aut.ac.nz* , 921 9999 ext 8044.

Whom do I contact for further information about this research?

Researcher Contact Details:

You can contact the research team if you want further information.

Nada Signal 921 9999 ext 7062 /email nada.signal@aut.ac.nz

Gwyn Lewis 921 9999 ext 7621 gwyn.lewis@aut.ac.nz

Appendix G.   TMS Study Consent Form

Consent Form

AUT
UNIVERSITY

Project title: **The reliability of Transcranial Magnetic Stimulation derived measures of cortical excitability during walking in healthy subjects and people with stroke.**

Project Supervisor: **Denise Taylor**

Researcher: **Nada Signal**

O   I have read and understood the information provided about this research project in the Information Sheet dated dd mmmm yyyy.

O   I have had an opportunity to ask questions and to have them answered.

O   I understand that I may withdraw myself or any information that I have provided for this project at any time prior to completion of data collection, without being disadvantaged in any way.

O   I agree to take part in this research.

O   I wish to receive a copy of the report from the research (please tick one): Yes O   No O

Participant's signature:
....

Participant's name:
....

Participant's Contact Details (if appropriate):

....

....

....

....

Date:

Note: The Participant should retain a copy of this form

Appendix H.   TMS Checklist

**Participant Checklist for using
Transcranial Magnetic Stimulation**

AUT
UNIVERSITY
TE WĀNANGA ARONUI O TĀMAKI MAKAU RAU

Volunteer Name:_____

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

Has the volunteer ever been diagnosed with epilepsy or
suffered from epileptic seizures?   Yes / No

Does the volunteer wear a pacemaker?   Yes / No

Does the volunteer have a metal implant in any part of their
body including the head (except tooth fillings)?   Yes / No

Has the volunteer ever had a skull fracture?   Yes / No

Does the volunteer have any known skull defects?   Yes / No

Does the volunteer suffer from recurring headaches? Yes / No

Has the volunteer suffered a head injury or concussion
within the last 6 months?   Yes / No

Does the volunteer suffer from anxiety associated with
medical procedures, needles etc.?   Yes / No

Checklist completed by: _____

Signature: _____

Appendix I.   Pilot Study Ethics Approval

28 July 2010

Ms Nada Signal
School of Rehabilitation & Occupation Studies
Auckland University of Technology
PB 92 006
Auckland 1142

Dear Nada

Ethics ref:	**NTX/10/07/069** (please quote in all correspondence)
Study title:	**Strength for task training to optimise locomotor function following stroke: a pilot randomised controlled trial; PIS/Cons V#21, 20/7/10**
Principal Investigator:	Ms Nada Signal
Co-Investigators:	A/Prof Denise Taylor (Supervisor), Prof Kathryn McPherson, Dr Gwyn Lewis, A/Prof Mark Weatherall, Dr Suzie Mudge, Ms Nicola Kayes, Ms Liz Binns
Localities:	Stroke Foundation, AUT University, Waitemata DHB

Thank you for sending in the Committee's requirements.   This study has now been given ethical approval by the Northern X Regional Ethics Committee   A list of members of the Committee is attached.

Approved Documents
- Information Sheet/Consent Form V#2 dated 20 June 2010
- Calendar Instructions V#1 dated 20 June 2010
- Table 1, Outcome Measures, V#1 dated 20 June 2010
- Descriptions of the interventions V#1 dated 20 June 2010 (2)
- Testing Protocol V#1 dated 20 June 2010
- Interview Guide V#1 dated 20 June 2010
- Screening Tools V#1 dated 20 June 2010
- Outcome Measures V#1 dated 20 June 2010
- Risk Assessment V#1 dated 20 June 2010
- Newspaper/newsletter advertisement V#1 dated 20 June 2010

This approval is valid until 1 August 2012, provided that Annual Progress Reports are submitted (see below).

Access to ACC

For the purposes of section 32 of the Accident Compensation Act 2001, the Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out   Participants injured as a result of treatment received in this trial will therefore be eligible to be considered for compensation in respect of those injuries under the ACC scheme.

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Appendix J.   Clinical Trial Registration

ANZCTR

Questions in **bold** text are mandatory. (*)

Request Number:	335568
Current Page:	Review

Trial from ANZCTR

Trial ID	ACTRN12610000460000
Trial Status:	Registered
Date Submitted:	1/06/2010
Date Registered:	4/06/2010
	Prospectively registered

Page 1

Public title	'Strength for Task Training' to improve walking following stroke.
Study title in 'Participant-Intervention-Comparator- Outcome (PICO)' format	'Strength for Task Training' to optimise locomotor function following stroke: A pilot randomised controlled trial.
Secondary ID [1]	N/A
UTN	
Trial acronym	

Page 2

Health condition(s) or problem(s) studied:	
Stroke	

Condition category:	Condition code:
Stroke	Ischaemic
Stroke	Haemorrhagic

Page 3

Descriptions of intervention(s) / exposure	Strength for Task Training Administered 3-9 months post- first stroke Group exercise 5 participants : 1 physiotherapist and 1 therapy assistant High intensity progressive resistance strength training of a prime mover immediately followed by motor skill training of a relevant motor skill task. Frequency: 3 times per week, 1 hour per session Duration: 12 weeks Intensity: 50-80% 1 Repetition Maximum and at 'somewhat hard'
Intervention Code:	Rehabilitation
Comparator / control treatment	1) Progressive Resistance Strength Training Administered 3-9 months post- first stroke Group exercise 5 participants : 1 physiotherapist and 1 therapy assistant High intensity progressive resistance strength training Frequency: 3 times per week, 1 hour per session Duration: 12 weeks Intensity: 50-80% 1RM 2) Motor Skill Training Administered 3-9 months post- first stroke Group exercise 5 participants : 1 physiotherapist and 1 therapy assistant High intensity motor skill training of relevant locomotor skills. Frequency: 3 times per week, 1 hour per session Duration: 12 weeks Intensity: 'somewhat hard' as rated by the participant 3) Usual Care Control 3-9 months post- first stroke No attempt to control the type or amount of rehabilitation recieved. Therapy specifics documented using previously tested methods.
Control group	Active

Page 4

Primary Outcome:	Neural Plasticity: Cortical excitability using Transcranial Magnetic Stimulation (TMS) of the soleus muscle at 10% Maximal Voluntary Contraction to measure Active Motor Threshold, Motor Evoked Potential, Intra cortical Inhibition and Intra cortical facilitation, Input/Output curves

	and during the push off phase of gait to measure task specific Motor Evoked Potential, Intra cortical Inhibition and Intra cortical facilitation
Timepoint:	Baseline Post-Intervention (12 weeks)
Primary Outcome:	Locomotor Function measured using comfortable and fast paced gait velocity, stair ascend and descend, 30second chair stand test and the step test
Timepoint:	Baseline Post-Intervention (12 weeks)
Primary Outcome:	Participation using the Subjective Index of Physical and Social Outcome and the Stroke Impact Scale
Timepoint:	Baseline Post-Intervention (12 weeks)
Secondary Outcome:	Recruitment numbers including the number of approached, screened and consented individuals over the recruitment phase
Timepoint:	Post-Intervention (12 weeks)
Secondary Outcome:	Randomised Controlled Trial Protocol Integrity including the number of completed versus scheduled intervention sessions, the number of exercise progressions over the intervention and the number of missing data points
Timepoint:	Post-Intervention (12 weeks)
Secondary Outcome:	Intervention acceptability including the barriers and facilitators to engaging in the rehabilitation intervention, the acceptability of the intervention and the perceived cost-benefit using semi-structured interviews
Timepoint:	Post-Intervention (12 weeks)
Secondary Outcome:	Muscle Strength measured using 1 Repetition Maximum leg press
Timepoint:	Baseline Post-Intervention (12 weeks)
Secondary Outcome:	Neural Plasticity: Brain Derived Neurotrophic Factor (BDNF) measured pre, during and post a bout of submaximal exercise using blood serum levels established via Enzyme-linked Immunosorbent assay (ELISA) kits
Timepoint:	Baseline Post-Intervention (12 weeks)

Page 5

Key Inclusion criteria	All people aged over 18 years with a single disabling supratentorial ischaemic stroke or intracerebral haemorrhage (Rankin 2-3); between 3-9 months post stroke at the start of the intervention; with a gait speed of between 0.05m/s −<1.2m/s at entry to the study; who are able to walk with or without aid and with or without standby assistance will be eligible for recruitment.
Minimum age	18 Years
Maximum age	No limit
Gender	Both males and females
Healthy volunteers?	No
Key exclusion criteria	Individuals will be excluded if: (a) their behaviour would interfere with participation in a group setting, as noted during initial assessment (e.g., agitation, aggression); (b) they have a significant cognitive deficit ((Mini-Mental State Examination (MMSE) Score <23); (c)they are unable to follow a 1 step English verbal command; (d) they are unable to give informed consent; (e) they are medically unstable in the opinion of a medical clinician; (f) they are participating in another study that, in the opinion of the investigator, may affect gait speed or add significantly to participant's burden; (g) they have excessive pain in any joint that could limit participation; or (h) they have another condition that could impact results (e.g., substance abuse, significant mental illnesses such as major depression) (i) they have any contra-indications to TMS, including pacemaker, artificial heart valves, other metal implants, pregnancy, skull abnormalities, history of seizures or epilepsy, taking medications that may lower seizure threshold, or claustrophobia.

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Study type	Interventional
Purpose of the study	Treatment
Allocation to intervention	Randomised controlled trial
Describe the procedure for enrolling a subject and allocating the treatment (allocation concealment procedures)	Potentially eligible stroke survivors will be approached via the Stroke Clinics of the Waitemata District Health Boards (DHB). Additional participants may be sourced from the Stroke Foundation, and directly from the community via newspaper advertisement. A research assistant will liaise with clinical staff and screen hospital databases, where available, to identify potential participants. The study research assistant will send an information sheet to all potential participants explaining the study and asking them if they would like to participate in the study. About one week later all potential participants will be contacted by telephone (or letter, where telephone is unavailable) to answer any questions and ascertain the persons willingness to participate. Once the project team are notified of potential participants, informed written consent will be sought. Only people who meet the eligibility criteria and provide written informed consent will be included. Once initial assessment is completed by a blinded assessor, participants will be randomly assigned to either the Strength for Task Training (STT), Progressive Resisted Strength Training (PRST), Motor Skill Training (MST),

	or Usual Care Control (UCC) group. Randomisation will be concealed using an on-line randomisation service based at the School of Rehabilitation and Occupation Studies, AUT University.
Describe the methods used to generate the sequence in which subjects will be randomised (sequence generation)	Randomised participants will receive the intervention once a group of 5 participants has accrued. Randomisation will be concealed using an on-line randomisation service based at the School of Rehabilitation and Occupation Studies, AUT University.
Masking / blinding	Blinded (masking used)
Who is / are masked / blinded (choose all that apply)	
Assignment	Parallel
Other design features	This mixed method study will involve a randomised controlled pilot trial design with four intervention groups to investigate the effect of STT on participation, locomotor function and neural plasticity in twenty people aged over 18 years with a single stroke and to consider the feasibility of the research protocol for a larger randomised controlled trial. Outcome measures of participation, locomotor function and neural plasticity, and semi-structured interviews to explore the feasibility and acceptability of the intervention, will be conducted prior to and post intervention. In addition the success of the sampling and recruitment strategy and the integrity of the trial protocol will be monitored using specific markers of success.
Type of endpoint (s)	Safety/efficacy
Statistical Methods/Analysis	

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Phase	Not Applicable
Anticipated date of first participant enrolment	1/09/2010
Date of first participant enrolment	
Anticipated date last participant recruited/enrolled	
Actual date last participant recruited/enrolled	
Target sample size	20
Recruitment status	Not yet recruiting

Recruitment in Australia

Recruitment state(s)	

Recruitment outside Australia

Country:	New Zealand
State/Province:	Auckland

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Funding Source:	Government body
Name:	Strategy to Advance Research Grant (STAR Grant) from Tertiary Education Commission's Building Research Capability in Strategically Relevant Areas (BRCSRA) fund
Address:	STAR Project School of Nursing Faculty of Medical and Health Sciences The University of Auckland Private Bag 92019 Auckland Mail Centre
Country:	New Zealand
Primary Sponsor	University
Name:	AUT University
Address:	School of Rehabilitation and Occupation Studies AUT University Private Bag 92006 Auckland 1142
Country:	New Zealand
Secondary Sponsor:	None
Name:	N/A

| Address: | N/A |
| Country: | |

Has the study received approval from at least one Ethics Committee?	No
Ethics Committee name:	
Address:	
Country:	
Approval Date:	
Submitted Date:	15/06/2010
HREC:	
Brief summary	Stroke is the most common cause of walking disability for New Zealanders. We know that improvements in walking are important for community participation and improved quality of life for people with stroke and this makes walking a very important focus of rehabilitation. When strength training is used to rehabilitate walking in people with stroke there are no improvements in walking ability. Whilst motor skill training studies show a modest improvement in walking, gains are still very limited. There is evidence that strength training followed immediately by practice of a specific motor skill may give better results. We expect our combination of strength training immediately followed by motor skill training (Strength for Task Training) will lead to improved walking. We will use a pilot study to determine if Strength for Task Training (STT) has potential as an effective rehabilitation strategy to improve walking ability in people following stroke and to establish the feasibility of the research methods planned to conduct a larger Randomised Clinical Trial.
Trial website	
Trial related presentations / publications	
Public Notes	

Principal Investigator

Title:	
Name:	
Address:	
Country:	
Tel:	
Fax:	
Email:	

Contact person for public queries

Title:	
Name:	Nada Signal
Address:	School of Rehabilitation and Occupation Studies AUT University Private Bag 92006 Auckland 1142
Country:	New Zealand
Tel:	+64 9 9219999 extn 7062
Fax:	
Email:	nada.signal@aut.ac.nz

Contact person for scientific queries

Title:	
Name:	Nada Signal
Address:	School of Rehabilitation and Occupation Studies AUT University Private Bag 92006 Auckland 1142
Country:	New Zealand
Tel:	+64 9 9219999 extn 7062
Fax:	
Email:	nada.signal@aut.ac.nz

Contact person responsible for updating information

| Title: | |
| Name: | Nada Signal |

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Appendix K. Pilot Study Ethics Amendment 1

28 July 2010

Ms Nada Signal
School of Rehabilitation & Occupation Studies
Auckland University of Technology
PB 92 006
Auckland 1142

Dear Nada

Ethics ref:	**NTX/10/07/069** (please quote in all correspondence)
Study title:	**Strength for task training to optimise locomotor function following stroke: a pilot randomised controlled trial: PIS/Cons V#21, 20/7/10**
Principal Investigator:	Ms Nada Signal
Co-Investigators:	A/Prof Denise Taylor (Supervisor), Prof Kathryn McPherson, Dr Gwyn Lewis, A/Prof Mark Weatherall, Dr Suzie Mudge, Ms Nicola Kayes, Ms Liz Binns
Localities:	Stroke Foundation, AUT University, Waitemata DHB

Thank you for sending in the Committee's requirements.   This study has now been given ethical approval by the Northern X Regional Ethics Committee . A list of members of the Committee is attached.

<u>Approved Documents</u>
— Information Sheet/Consent Form V#2 dated 20 June 2010
— Calendar Instructions V#1 dated 20 June 2010
— Table 1, Outcome Measures, V#1 dated 20 June 2010
— Descriptions of the interventions V#1 dated 20 June 2010 (2)
— Testing Protocol V#1 dated 20 June 2010
— Interview Guide V#1 dated 20 June 2010
— Screening Tools V#1 dated 20 June 2010
— Outcome Measures V#1 dated 20 June 2010
— Risk Assessment V#1 dated 20 June 2010
— Newspaper/newsletter advertisement V#1 dated 20 June 2010

This approval is valid until 1 August 2012, provided that Annual Progress Reports are submitted (see below).

<u>Access to ACC</u>
For the purposes of section 32 of the Accident Compensation Act 2001, the Committee is satisfied that this study is not being conducted principally for the benefit of the manufacturer or distributor of the medicine or item in respect of which the trial is being carried out. Participants injured as a result of treatment received in this trial will therefore be eligible to be considered for compensation in respect of those injuries under the ACC scheme.

<u>Amendments and Protocol Deviations</u>
All significant amendments to this proposal must receive prior approval from the Committee. Significant amendments include (but are not limited to) changes to:
— the researcher responsible for the conduct of the study at a study site
— the addition of an extra study site
— the design or duration of the study
— the method of recruitment
— information sheets and informed consent procedures.

Significant deviations from the approved protocol must be reported to the Committee as soon as possible.

<u>Annual Progress Reports and Final Reports</u>
The first Annual Progress Report for this study is due to the Committee by **29 July 2011**. The Annual Report Form that should be used is available at www.ethicscommittees.health.govt.nz. Please note that if you do not provide a progress report by this date, ethical approval may be withdrawn.

A **Final Report** is also required at the conclusion of the study. The Final Report Form is also available at www.ethicscommittees.health.govt.nz.

<u>Requirements for the Reporting of Serious Adverse Events (SAEs)</u>
SAEs occurring in this study must be individually reported to the Committee within 7-15 days only where they:
— are *unexpected* because they are not outlined in the investigator's brochure, and
— are not defined study end-points (e.g. death or hospitalisation), and
— occur in patients located in New Zealand, and
— if the study involves blinding, result in a decision to break the study code.

Please see www.ethicscommittees.health.govt.nz for more information on the reporting of SAEs, and to download the SAE Report Form.

We wish you all the best with your study.

Yours sincerely

Pat Chainey
Administrator
Northern X Regional Ethics Committee
Email: pat_chainey@moh.govt.nz

G. Grinter: AUT Research Office

Appendix L. Pilot Study Ethics Amendment 2

Health
and
Disability
Ethics
Committees

Northern X Regional Ethics Committee
c/- Ministry of Health
650 Great South Rd
Penrose
Auckland
Phone: (09) 580 9105
Email: northernx_ethicscommittee@moh.govt.nz

23 September 2011

Ms Nada Signal
Auckland University of Technology
School of Rehabilitation & Occupation Studies
Aucklan University of Technology
PB 92 006
Auckland 1142

Dear Nada

Ethics ref:	NTX/10/07/069 (please quote in all correspondence)
Study title:	Strength for task training to optimise locomotor function following stroke: a pilot randomised controlled trial:Prot/amend 25/08/10: PIS/Cons V#1, 5/09/2011
Principal investigator:	Nada Signal

Thank you for your letter received 14 September 2011.

The amendments were reviewed by the Deputy Chairperson of the Northern X Regional Ethics Committee under delegated authority.

Ethical approval has been given for:
- Participants information/Consent form: (version 1, dated 5/09/2011)
- Clinical Debriefing Guide (version 1, dated 5/09/2011)
    - Conduct a one hour clinical debriefing with the physiotherapists

Yours sincerely

Sabrina Young
Temp Administrator
Northern X Regional Ethics Committee

Appendix M. Pilot Study Information Sheet

Rehabilitation to improve walking following stroke

Principal Investigator	Nada Signal	Phone: (09) 921 9999 x7062
Supervisors	Denise Taylor Kathryn McPherson Gwyn Lewis	Phone: (09) 921 9680 Phone: (09) 921 9999 x7110 Phone: (09)921 9999 x7621
Co-Investigators	Liz Binns Suzie Mudge Nicola Kayes Mark Weatherall	Phone: (09) 921 9785 Phone: (09) 921 9999 x7096 Phone: (09) 921 9999 x7309 Phone: (04) 385 5999 x4817

Invitation

Kia ora, talofa lava and hello, you are invited to take part in a study aiming to explore the effects of different of rehabilitation approaches to improve walking abilities after stroke. Please remember that:

- Your participation in this study is entirely voluntary (your choice). You do not have to take part in this study.
- If you do agree to take part you are free to withdraw at any time, without having to give a reason. This will in no way affect your current or future health care.
- Participation in this study will be stopped should any harmful effects appear or if the doctor feels it is not in your best interests to continue.

This information sheet will explain the research study. Please feel free to ask about anything you do not understand or if you have questions at any time.

What is the purpose of the study?

This study is part of an ongoing programme of research investigating rehabilitation approaches to improve walking after stroke, and is part of Nada Signal's doctoral studies.

We want to:
a) Explore whether different rehabilitation approaches have potential to improve walking ability in people following stroke
b) Find out the barriers and facilitators to high intensity rehabilitation in people following stroke
c) See whether people with stroke believe it is worth their effort to participate in different rehabilitation approaches
d) Consider the feasibility of carrying out a much bigger research study comparing different rehabilitation approaches to improve walking in a large group of people with stroke.

How are people chosen to be asked to be part of the study?

People are being invited to participate in the research study if they meet all the following criteria:
1) Aged over 18 years
2) Have had a single stroke more than 3 months ago
3) Are able to walk, but still have difficulty with walking since the stroke.

People may be excluded from taking part in the study if:
1) they are unable to participate in a group rehabilitation setting
2) they are considered medically unsuitable to participate
3) the researchers are unable to reliably record one of the study outcome measures

Twenty people will participate in the study.

What happens in the study?

The study involves being assessed using a variety of measures, completing a twelve week rehabilitation programme, and then being assessed again. After the first set of assessments each person is assigned by chance, using a computer, to one of four groups (A, B, C or D).

The Rehabilitation Programmes:

The rehabilitation programmes last for twelve weeks. People in Groups B, C and D will come to the North Shore campus of AUT University to do their rehabilitation. This will involve three, one hour sessions per week for twelve weeks. The total time spent doing the rehabilitation in Groups B, C and D is 36 hours. The rehabilitation will be done in a group of five people and will be supervised by a physiotherapist and a therapy assistant.

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What is the purpose of the study?

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We want to:
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   b) Find out the barriers and facilitators to high intensity rehabilitation in people following stroke
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conducted in a group setting, participants may also develop a network of friends and support as a result of participating.

People who take part in this study are acting as co-researchers and will contribute to our understanding of the barriers and facilitators to taking part in rehabilitation and the acceptability of specific approaches. Their contribution will aid the development rehabilitation approaches that are responsive to the needs of people with walking disability following stroke.

What are the risks of participating?

The Study:

This study asks participants for a significant commitment of time and energy. People with stroke may experience some fatigue due to the amount and nature of this commitment. Participants are able to terminate an experimental or rehabilitation session at any stage and the researchers and physiotherapists will monitor all sessions closely.

Rehabilitation Interventions:

There is a chance (1:4) that you will be assigned to Group A, and therefore not receive rehabilitation at AUT University during the study, some people may feel disappointed about this. Anyone who is assigned to Group A may choose, at the end of the study, to come to the Physiotherapy Clinic at AUT University to complete a further 12 week rehabilitation programme. If the outcome of the study is positive the researchers will suggest that the rehabilitation is similar to what participants in Groups B, C or D received. If you choose to do this there is no charge for the rehabilitation, although you will need to cover your own transport costs.

Those participants in Group B, C or D will train at a high intensity, three times a week for twelve weeks. Participants may find the programme physically demanding and may experience the fatigue and physical discomfort that is sometimes associated with starting a new exercise regime. This risk is minimised as the exercise intensity is determined based on the individuals' abilities and fitness, is gradually increased over the first two weeks, and exertion levels and technique are closely monitored by the physiotherapist. Participants are able to terminate a rehabilitation session at any stage.

Measurement of Brain Excitability using Transcranial Magnetic Stimulation:

Transcranial Magnetic Stimulation is painless; however it does cause the muscles to twitch, makes a clicking noise and involves the researchers touching the participants head. Some people find this uncomfortable. The intensity of the magnetic stimulator will begin at a very low level, allowing participants time to get used to the muscle twitches, and ear plugs will be offered.

It is recommended that certain people do not have transcranial magnetic stimulation, either because there is a slightly increased risk of seizure with it or because its effects are not known in that group. This includes people with metal implants in their head and neck, pacemakers, skull fractures, pregnant women, people who take medication

conducted in a group setting, participants may also develop a network of friends and support as a result of participating.

People who take part in this study are acting as co-researchers and will contribute to our understanding of the barriers and facilitators to taking part in rehabilitation and the acceptability of specific approaches. Their contribution will aid the development rehabilitation approaches that are responsive to the needs of people with walking disability following stroke.

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The Study:

This study asks participants for a significant commitment of time and energy. People with stroke may experience some fatigue due to the amount and nature of this commitment. Participants are able to terminate an experimental or rehabilitation session at any stage and the researchers and physiotherapists will monitor all sessions closely.

Rehabilitation Interventions:

There is a chance (1:4) that you will be assigned to Group A, and therefore not receive rehabilitation at AUT University during the study, some people may feel disappointed about this. Anyone who is assigned to Group A may choose, at the end of the study, to come to the Physiotherapy Clinic at AUT University to complete a further 12 week rehabilitation programme. If the outcome of the study is positive the researchers will suggest that the rehabilitation is similar to what participants in Groups B, C or D received. If you choose to do this there is no charge for the rehabilitation, although you will need to cover your own transport costs.

Those participants in Group B, C or D will train at a high intensity, three times a week for twelve weeks. Participants may find the programme physically demanding and may experience the fatigue and physical discomfort that is sometimes associated with starting a new exercise regime. This risk is minimised as the exercise intensity is determined based on the individuals' abilities and fitness, is gradually increased over the first two weeks, and exertion levels and technique are closely monitored by the physiotherapist. Participants are able to terminate a rehabilitation session at any stage.

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It is recommended that certain people do not have transcranial magnetic stimulation, either because there is a slightly increased risk of seizure with it or because its effects are not known in that group. This includes people with metal implants in their head and neck, pacemakers, skull fractures, pregnant women, people who take medication

which lowers seizure threshold and people with a history of epilepsy. All participants will be screened using a TMS Safety screening questionnaire and strict adherence to the exclusion criteria will minimise any risk.

During TMS testing small areas of skin on the leg need to be shaved, abraded and wiped with alcohol before adhesive electrodes can be attached. This can cause a temporary stinging sensation and may cause minor, temporary skin reddening.

Some of the TMS is carried out while the participant walks on a treadmill. This is potentially physically demanding for people with stroke. In addition, some people feel they may trip on the treadmill. Trips and falls will be prevented by: a) having participants will walk at their comfortable pace, b) taking regular rests, c) holding onto a safety rail and d) attaching participants to an overhead safety system via a body harness to prevent falls.

Blood Tests:

Some people find the process of needle insertion for blood testing uncomfortable; this is similar to having your blood taken for a routine blood test. An experienced phlebotomist who is certified in venous cannulation will be taking the blood samples to minimise discomfort.

During the blood tests participants will exercise on a stationary bike at a submaximal intensity. This may be physically demanding, particularly if the participant does not exercise on a regular basis. As the exercise intensity is determined by the participant this is likely to be a minimal risk. Participants are able to terminate an experimental session at any stage.

Compensation:

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation, and Compensation Act 2001. ACC cover is not automatic, and your case will need to be assessed by ACC according to the provisions of the Injury Prevention, Rehabilitation, and Compensation Act 2001. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors, such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses, and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, contact your nearest ACC office or the investigator.

You are also advised to check whether participation in this study would affect any indemnity cover you have or are considering, such as medical insurance, life insurance and superannuation.

What are the costs of taking part in this study?

There should not be any cost to you, except the time and effort you choose to contribute. We will reimburse travels costs for your visits to and from the North Shore campus of AUT University, up to a value of $40.00 per round trip.

How will my privacy be protected?

Each participant will be assigned a specific code which is used to identify them on all documentation, rather than using their name. All data will be stored in a locked cabinet. Consent forms containing any identifying information will be kept separate from raw data in a second locked cabinet. Only members of the research team directly involved in data collection/analysis will have access to raw data.

What will happen with the results?

The study findings will be submitted for publication in peer reviewed international rehabilitation journals. Presentations of the data will be made at national and international clinical and scientific meetings. In the future we also intend to use free web-based packages, aimed at training physiotherapists to deliver the programme in clinical practice.

Will I be able to have a copy of the results?

At the end of the study, all participants will receive a summary of the findings, along with an opportunity to discuss the findings with a researcher. All participants will also be offered an opportunity to attend a meeting/hui to discuss the findings.

If you have any concerns or questions?

If you have any questions please feel free to contact one of the researchers listed at the top of this information sheet.

If you have any queries or concerns regarding your rights as a participant in the study, you may wish to contact an independent health and disability advocate:
Free phone: 0800 555 050
Free fax: 0800 2 SUPPORT (0800 2787 7678)
Email: advocacy@hdc.org.nz

Seeking Cultural Support:

The researchers acknowledge the importance of spiritual health (Taha wairua), mental health (Taha hinengaro), family health (Taha whanau), and physical health (Taha tinana) in a person's overall health and well being. This research has the potential to be physically, mentally and/or spiritually demanding for some people;

and some of the assessments involve the researchers taking blood samples or touching the participant's head. The researchers welcome and encourage family/whanau/friends to be present at all research and rehabilitation sessions.

To ensure ongoing cultural safety Nga Kai Tataki - Maori Research Review Committee Waitemata DHB encourage those who identify themselves as Maori and who are participating in health research or clinical trials to seek cultural support and advice from either Mo Wai Te Ora – Maori Health Services or their own Kaumatua or Whaea. For assistance please contact the Services Clinical Leader for Mo Wai Te Ora – Maori Health on 09 486 1491 ext: 2324 or the Maori Research Advisor on 09 486 1491 ext: 2553

Statement of Ethical Approval

This study has received ethical approval from the Northern X Regional Ethics Committee.

Appendix N. Pilot Study Consent Form

AUT
U N I V E R S I T Y
TE WĀNANGA ARONUI O TĀMAKI MAKAU RAU

Consent Form

Rehabilitation to improve walking
following stroke

Principal Investigator	Nada Signal	Phone: (09) 921 9999 x7062
Supervisors	Denise Taylor Kathryn McPherson Gwyn Lewis	Phone: (09) 921 9680 Phone: (09) 921 9999 x7110 Phone: (09)921 9999 x7621
Co-Investigators	Liz Binns Suzie Mudge Nicola Kayes Mark Weatherall	Phone: (09) 921 9785 Phone: (09) 921 9999 x7096 Phone: (09) 921 9999 x7309 Phone: (04) 385 5999 x4817

Request for interpreter

English	I wish to have an interpreter	Yes	No
Deaf	I wish to have a NZ sign language interpreter	Yes	No
Māori	E hiahia ana ahau ki tetahi kaiwhaka Māori/kaiwhaka pakeha korero	Ae	Kao
Cook Island Māori	Ka inangaro au i tetai tangata uri reo	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu	E	Nakai
Sāmoan	Ou te mana'o ia i ai se fa'amatala upu	Ioe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania ki na gagana o na motu o te Pahefika	Ioe	Leai
Tongan	Oku ou fiema'u ha fakatonulea	Io	Ikai

I have read and I understand the information sheet dated 25 August 2010 for volunteers taking part in the study designed to investigate rehabilitation approaches to improve walking after stroke. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.	Yes	No
I have had the opportunity to use whānau support or a friend to help me ask questions and understand the study.	Yes	No
I know who to contact if I have any questions about the study in general.	Yes	No
I understand that taking part in this study is voluntary (my choice), and that I may withdraw from the study at any time, and this will in no way affect my future or continuing health care	Yes	No
I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.	Yes	No
I understand that the treatment, or investigation, will be stopped if it should appear harmful to me.	Yes	No
I understand the compensation provisions for this study.	Yes	No
I have had time to consider whether to take part in the study.	Yes	No
I know who to contact if I have any side effects from the study.	Yes	No
I consent to my blood samples being sent to Diagnostic Medical Laboratories Limited.	Yes	No
I consent to my blood samples being disposed of at the end of the study.	Yes	No
I would like a karakia (blessing) to be offered before my blood samples are disposed of at the end of the study	Yes	No
I consent to my interviews being audiotaped.	Yes	No
I would like the audiotape of my interview returned to me when the study is complete.	Yes	No
I wish to receive a copy of the results.	Yes	No

I would like the researcher to discuss the outcomes of the study with me.	Yes	No
I agree to my GP or other current provider being informed of my participation in this study.	Yes	No
I am aware that I may be excluded from participation in the study for any of the following reasons: a) An impairment or medical condition which would interfere with participation in a group setting b) An impairment or medical condition which could impact the results of the study c) A medical condition which contraindicates high intensity rehabilitation d) A medical condition which contraindicates Transcranial magnetic stimulation or blood sampling. e) Participation in another study that, in the opinion of the researcher, may affect the results of this study f) The researchers are unable to reliably record one of the study outcome measures	Yes	No

I _____ (full name) hereby consent to take part in this study.

Date:

Signature:

Project explained by:

Project role:

Signature:

Date: